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

Geneen LJ, Dorée C, Estcourt LJ

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[Intervention Review]

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

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ABSTRACT

Background

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

Objectives

To identify and assess the effectiveness of different types of interventions (psychological and psychosocial, educational, medication interventions, or multi-component interventions) and interventions specific to different age groups, to improve adherence to iron chelation therapy compared to another listed intervention, or standard care in people with SCD or thalassaemia.

Search methods

We searched CENTRAL (Cochrane Library), MEDLINE, PubMed, Embase, CINAHL, PsycINFO, ProQuest Dissertations & Global Theses, Web of Science & Social Sciences Conference Proceedings Indexes and ongoing trial databases (13 December 2021). We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register (1 August 2022).

Selection criteria

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

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

Data collection and analysis

For this update, two authors independently assessed trial eligibility and risk of bias, and extracted data. We assessed the certainty of the evidence using GRADE.

Main results

We included 19 RCTs and one NRSI published between 1997 and 2021. One trial assessed medication management, one assessed an education intervention (NRSI) and 18 RCTs were of medication interventions. Medications assessed were subcutaneous deferoxamine, and two oral chelating agents, deferiprone and deferasirox.

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

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

We identified nine comparisons of interest.

1. Deferiprone versus deferoxamine

We are uncertain whether or not deferiprone affects adherence to iron chelation therapy (four RCTs, unpooled, very low-certainty evidence), all-cause mortality (risk ratio (RR) 0.47, 95% confidence interval (CI) 0.18 to 1.21; 3 RCTs, 376 participants; very low-certainty evidence), or serious adverse events (SAEs) (RR 1.43, 95% CI 0.83 to 2.46; 1 RCT, 228 participants; very low-certainty evidence).

Adherence was reported as "good", "high" or "excellent" by all seven trials, though the data could not be analysed formally: adherence ranged from 69% to 95% (deferiprone, mean 86.6%), and 71% to 93% (deferoxamine, mean 78.8%), based on five trials (474 participants) only.

2. Deferasirox versus deferoxamine

We are uncertain whether or not deferasirox affects adherence to iron chelation therapy (three RCTs, unpooled, very low-certainty evidence), although medication adherence was high in all trials.

We are uncertain whether or not there is any difference between the drug therapies in serious adverse events (SAEs) (SCD or thalassaemia) or all-cause mortality (thalassaemia).

3. Deferiprone versus deferasirox

We are uncertain if there is a difference between oral deferiprone and deferasirox based on a single trial in children (average age 9 to 10 years) with any hereditary haemoglobinopathy in adherence, SAEs and all-cause mortality.

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

One RCT compared deferasirox in different tablet forms. There may be a preference for FCTs, shown through a trend for greater adherence (RR 1.10, 95% CI 0.99 to 1.22; 1 RCT, 88 participants), although medication adherence was high in both groups (FCT 92.9%; DT 85.3%). We are uncertain if there is a benefit in chelation-related AEs with FCTs.

We are uncertain if there is a difference in the incidence of SAEs, all-cause mortality or sustained adherence.

5. Deferiprone and deferoxamine combined versus deferiprone alone

We are uncertain if there is a difference in adherence, though reporting was usually narrative as triallists report it was "excellent" in both groups (three RCTs, unpooled).

We are uncertain if there is a difference in the incidence of SAEs and all-cause mortality.

6. Deferiprone and deferoxamine combined versus deferoxamine alone

We are uncertain if there is a difference in adherence (four RCTs), SAEs (none reported in the trial period) and all-cause mortality (no deaths reported in the trial period). There was high adherence in all trials.

7. Deferiprone and deferoxamine combined versus deferiprone and deferasirox combined

There may be a difference in favour of deferiprone and deferasirox (combined) in rates of adherence (RR 0.84, 95% CI 0.72 to 0.99) (one RCT), although it was high (> 80%) in both groups.

We are uncertain if there is a difference in SAEs, and no deaths were reported in the trial, so we cannot draw conclusions based on these data (one RCT).

8. Medication management versus standard care

We are uncertain if there is a difference in QoL (one RCT), and we could not assess adherence due to a lack of reporting in the control group.

9. Education versus standard care

One quasi-experimental (NRSI) study could not be analysed due to the severe baseline confounding.

Authors' conclusions

The medication comparisons included in this review had higher than average adherence rates not accounted for by differences in medication administration or side effects, though often follow-up was not good (high dropout over longer trials), with adherence based on a per protocol analysis.

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

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

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

PLAIN LANGUAGE SUMMARY

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

Review question

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

Background

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

Search date

The evidence is current to 1 August 2022.

Study characteristics

We searched the literature for both randomised and non-randomised trials, and found 19 randomised trials and one non-randomised trial, totalling 1525 participants, published between 1997 and 2021.

Key results

A total of 18 trials looked at drug interventions, one trial looked at a medication management intervention, and one assessed an education intervention (a non-randomised trial).

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

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

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

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

Two trials assessed non-medication interventions: one six-month trial of medication management reported very little usable data, and we cannot be certain of the impact of the intervention. The other trial assessing an education intervention was unbalanced, and the data did not allow a good comparison, therefore we were unable to use it.

Quality (certainty) of the evidence

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

Summary of findings 1. Summary of findings: Comparison 1 - deferiprone (DFP) versus deferoxamine (DFO)

Intervention: DFP

Comparison: DFO

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with DFO	Risk with DFP				
Adherence to iron chelation therapy (%, SD)	See comments.		—	612 (7 RCTs)	⊕◯◯◯ Very low[a,b,c]	2 trials (unpooled) provided analysable data (%, SD); the remaining trials reported only as % (or narratively), with no error (SD, or otherwise) and have been presented in Table 1 separately to the analyses.
Total reported SAEs (from therapy, disease, non-adherence)	184 per 1000	**263 per 1000** (153 to 453)	**RR 1.43** (0.83 to 2.46)	228 (1 RCT)	⊕◯◯◯ Very low[c,d]	—
All-cause mortality	75 per 1000	**35 per 1000** (13 to 91)	**RR 0.47** (0.18 to 1.21)	376 (3 RCTs)	⊕◯◯◯ Very low[a,c,e]	In a fourth trial, no events occurred in either arm (Pennell 2006).
Sustained adherence	See comments.		—	—	—	Sustained adherence is reported as adherence since all trials were longer than 6 months and only provided end of study adherence numbers.
QoL (assessed with CHQ-50 and SF-36) Follow-up mean 12 months	See comments.		—	(1 RCT)	⊕◯◯◯ Very low[d,f]	Data presented in additional tables from a single trial (Kwiatkowski 2021). No significant between-group change over time. Major bias due to missing data (over half) for outcomes (DFP: CHQ-50 n = 60/152 and SF-36 n = 35/152; DFO: CHQ-50 n = 23/76 and SF-36 n = 19/76).

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

CHQ-50: Child Health Questionnaire - 50 items; **CI**: confidence interval; **DFO**: deferoxamine; **DFP**: deferiprone; **MD**: mean difference; **QoL**: quality of life; **RCT**: randomised controlled trial; **RR**: risk ratio; **SAE**: serious adverse event; **SD**: standard deviation; **SF-36**: Short-Form Questionnaire - 36 items.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

[a]We downgraded the certainty of evidence once for risk of bias due to high or uncertain risk of bias in one or more domains.
[b]We downgraded the certainty of evidence twice for inconsistency due to considerable heterogeneity in the comparison.
[c]We downgraded the certainty of evidence twice for imprecision due to wide CIs and small sample size (not reaching the optimal information size).
[d]Downgraded twice due to high risk of bias in multiple domains, including blinding (detection bias), incomplete outcome data (attrition bias), and unclear risk of bias for selection bias and other (early termination).
[e]We downgraded the certainty of evidence once for indirectness as one trial was conducted in participants with thalassaemia intermedia only, a milder form of thalassaemia.
[f]Downgraded twice for imprecision due to small sample size (below optimal information size for this outcome).

Summary of findings 2. Summary of findings: Comparison 2 - deferasirox (DFX) versus deferiprone (DFO)

Intervention: DFX

Comparison: DFO

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with DFO	Risk with DFX				
Adherence to iron chelation therapy (%, SD)	See comments.			452 (3 RCTs)	⊕◯◯◯ Very low[a,b]	3 RCTs (n = 452) reported adherence, although 2 of these could not be analysed (Hassan 2016, n = 60; and Vichinsky 2007, n = 195). All 3 RCTs reported no significant difference between groups.
SAEs Thalassaemia-related SAEs	DFO: 83 per 1000	DFX: 79 per 1000 (34 to 179)	**RR 0.95** (0.41 to 2.17)	247 (2 RCTs)	⊕◯◯◯ Very low[a,b]	Zero cases reported in one RCT (n = 60, Hassan 2016), so data are based on a single trial (n = 187, Pennell 2014).
SAEs SCD-related SAEs	1 RCT (n = 195) reported SCD-related AEs as "pain crisis" and "other", so no overall estimate of effect (subtotals calculated using 99% CI)		—	195 (1 RCT)	⊕◯◯◯ Very low[a,b]	Data for sub-outcome "pain crisis", and sub-outcome "other", are presented in the main text, but we are unable to combine these data as there may be double-counting; we have therefore not presented the summary statistic in the SoF table.

						Sub-outcomes are presented using 99% CI instead of 95% CI.
All-cause mortality	8 per 1000	**8 per 1000** (1 to 128)	**POR 0.96** (0.06 to 15.42)	240 (2 RCTs)	⊕◯◯◯ Very low[a,b]	Both RCTs reporting this outcome were in people with thalassaemia only; zero cases in 1 RCT.
Sustained adherence	See comments.			—	—	Sustained adherence is reported as adherence since all studies were longer than 6 months and only reported end of study adherence.
QoL	Not reported.			—	—	—

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

AE: adverse event; **CI**: confidence interval; **DFO**: deferiprone; **DFX**: deferasirox; **POR**: Peto odds ratio; **QoL**: quality of life; **RCT**: randomised controlled trial; **RR:** risk ratio; **SAE**: serious adverse event; **SD**: standard deviation; **SoF:** summary of findings

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
[a]We downgraded the certainty of evidence twice due to high or uncertain risk of bias in several domains.
[b]We downgraded the certainty of evidence once due to imprecision as the CIs are wide and there is only one study with data in the comparison.

Summary of findings 3. Summary of findings: Comparison 3 - deferiprone (DFP) versus deferasirox (DFX)

Intervention: DFP **Comparison: DFX**						
Outcomes	**Anticipated absolute effects*** (95% CI)		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with DFX	**Risk with DFP**				
Adherence to iron chelation (%, SD) Follow-up: 12 months	The mean adherence to iron chelation	MD **3.00 % lower** (6.56 lower to 0.56 higher).	—	390 (1 RCT)	⊕⊕◯◯ Low[a]	95% adherence in DFX group as reported by Maggio 2020.

	(%, SD) was **95.00**%.					
SAE (chelation-related) (n/N) Follow-up: 12 months	20 per 1000	**31 per 1000** (9 to 100)	**POR 1.54** (0.44 to 5.39)	390 (1 RCT)	⊕◯◯◯ Very low[a,b]	—
Total SAEs Follow-up: 12 months	71 per 1000	**68 per 1000** (33 to 139)	**RR 0.95** (0.46 to 1.96)	390 (1 RCT)	⊕◯◯◯ Very low[a,b]	—
All-cause mortality (n/N) Follow-up: 12 months	0 per 1000	**0 per 1000** (0 to 0)	**RD 0.00** (-0.01 to 0.01)	390 (1 RCT)	⊕⊕◯◯ Low[c]	No deaths occurred during the study period, though the sample size was below the optimal information size to make any assessment of risk.
Sustained adherence	See comments.			—	—	Sustained adherence is reported as adherence as the study was 1 year in duration and end of trial adherence reported.
QoL	Outcome not reported.			—	—	—

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

AE: adverse event; **CI**: confidence interval; **DFP**: deferiprone; **DFX**: deferasirox; **POR**: Peto odds ratio; **QoL**: quality of life; **RCT**: randomised controlled trial; **RD:** risk difference; **RR**: risk ratio; **SAE**: serious adverse event; **SD**: standard deviation

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
[a]Downgraded twice for high risk of bias for blinding: may impact adherence, clinical decision-making or reporting of AEs (no impact on mortality).
[b]Downgraded twice for imprecision due to wide CIs.
[c]Downgraded twice for imprecision due to zero events in both arms. Below optimal information size.

Summary of findings 4. Summary of findings: Comparison 4 - deferasirox (DFX) film-coated tablets versus DFX dispersible tablets

Intervention: DFX film-coated tablet

Comparison: DFX dispersible tablet

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with DFX dispersible tablet	Risk with DFX film-coated tablet				
Adherence to iron chelation therapy (%, SD) Follow-up: 13 weeks	The mean adherence to iron chelation therapy (%, SD) was **84.3**%.	MD **5.00% higher** (6.75 lower to 16.75 higher)	—	91 (1 RCT)	⨁◯◯◯ Very low[a,b]	Mean 84.3% (95% CI 81.1 to 89.5) as reported by Taher 2017 in control (DFX dispersible tablet).
Sustained adherence to iron chelation therapy (%, SD) Follow-up: 24 weeks	The mean sustained adherence to iron chelation therapy (%, SD) was **82.9**%.	MD **7.00% higher** (8.94 lower to 22.94 higher)	—	54 (1 RCT)	⨁◯◯◯ Very low[a,b]	Mean 82.9% as reported in control group (dispersible tablet).
Incidence of SAEs	151 per 1000	**184 per 1000** (94 to 358)	**RR 1.22** (0.62 to 2.37)	173 (1 RCT)	⨁◯◯◯ Very low[a,c]	—
All-cause mortality	0 per 1000	**0 per 1000** (0 to 0)	**POR** 7.30 (0.14 to 368.15)	173 (1 RCT)	⨁◯◯◯ Very low[a,c]	—
QoL	Outcome not reported.			—	—	—

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

CI: confidence interval; **DFX**: deferasirox; **MD**: mean difference; **POR**: Peto odds ratio; **QoL**: quality of life; **RR**: risk ratio; **SAE**: serious adverse event; **SD**: standard deviation

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
[a]We downgraded the certainty of evidence twice for risk of bias due to high or unclear risk of bias in all domains.
[b]Downgraded twice for imprecision due to very wide confidence intervals and small study size (smaller than optimal information size).
[c]We downgraded the certainty of evidence once for imprecision due to wide CIs.

Summary of findings 5. Summary of findings: Comparison 5 - deferiprone (DFP) plus deferoxamine (DFO) versus DFP

Intervention: DFP plus DFO

Comparison: DFP

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with DFP	Risk with DFP plus DFO				
Adherence to iron chelation therapy (%, SD)	See comments.			369 (4 RCTs)	⊕⊕◯◯ Low[a]	4 RCTs reported adherence: 1 did not report by group, but stated compliance was similar (Badawy 2010, n = 100); 2 reported compliance as "excellent compliance" (Aydinok 2007, n = 20 and El Beshlawy 2008, n = 36); and 1 as % (SD) with no difference between groups (Maggio 2009, n = 213).
Incidence of SAEs	28 per 1000	**4 per 1000** (0 to 78)	**RR 0.15** (0.01 to 2.81)	213 (1 RCT)	⊕⊕◯◯ Low[b,c]	—
All-cause mortality	33 per 1000	**26 per 1000** (6 to 105)	**POR 0.77** (0.17 to 3.42)	237 (2 RCTs)	⊕◯◯◯ Very low[c,d]	—
Sustained adherence	Outcome not reported.			—	—	Sustained adherence is reported as adherence since trial duration was longer than 6 months and trials report adherence for the whole length of trial.
QoL	See comments.			—	—	QoL was either not reported or no validated instruments were used.

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

CI: confidence interval; **DFO**: deferoxamine; **DFP**: deferiprone; **POR**: Peto odds ratio; **QoL**: quality of life; **RCT**: randomised controlled trial; **RR:** risk ratio; **SD:** standard deviation

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

[a]We downgraded the certainty of evidence twice for risk of bias as there was high or uncertain risk of bias in most domains in three out of four trials.
[b]We downgraded the certainty of evidence once due to high or unclear risk of bias in three domains.
[c]We downgraded the certainty of evidence once for imprecision due to wide CIs.
[d]We downgraded the certainty of evidence twice for risk of bias as there was high or uncertain risk of bias in one trial in this comparison.

Summary of findings 6. Summary of findings: Comparison 6 - deferiprone (DFP) plus deferoxamine (DFO) versus DFO

Intervention: DFP plus DFO **Comparison: DFO**						
Outcomes	**Anticipated absolute effects*** (95% CI)		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with DFO	**Risk with DFP plus DFO**				
Adherence to iron chelation therapy (%, SD)	See comments.			281 (5 RCTs)	⨁⨁◯◯ Low[a]	5 RCTs reported adherence/compliance at approx 1 year: 2 RCTs did not report by group, simply stating "no statistical difference" (Badawy 2010, n = 100) and "excellent" (El Beshlawy 2008, n = 38); 1 RCT only reported compliance for the combined group (Galanello 2006a, n = 60); 1 RCT reported "excellent or good in all 11 (combined) and 14 (DFX only) participants" that were analysed (Mourad 2003, n = 25); and 1 RCT reported by group as "no significant difference" (Tanner 2007, n = 58).
Incidence of SAEs	See comments.			180 (4 RCTs)	⨁⨁◯◯ Low[a]	3 RCTs report zero SAEs; 1 RCT did not report SAEs. Badawy 2010 is not included in quantitative analysis
All-cause mortality	See comments.			—	—	No included trials reported death as an outcome. As AEs/SAEs were reported, we suspect no deaths occurred.
Sustained adherence	See comments.			—	—	Sustained adherence reported above as adherence since study duration was longer than 6 months and adherence reported at end of trial.
QoL	Outcome not reported.			—	—	—

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **DFO**: deferoxamine; **DFP**: deferiprone; **QoL**: quality of life; **RCT**: randomised controlled trial; **SAE**: serious adverse event; **SD**: standard deviation

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
[a]We downgraded the certainty of evidence twice for risk of bias as high or unclear risk of bias in all domains.

Summary of findings 7. Summary of findings: Comparison 7 - deferiprone (DFP) plus deferoxamine (DFO) versus DFP plus deferasirox (DFX)

Intervention: DFP plus DFO **Comparison: DFP plus DFX**						
Outcomes	**Anticipated absolute effects*** (95% CI)		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with DFP plus DFX	**Risk with DFP plus DFO**				
Adherence to iron chelation therapy rates (n, N) Follow-up 1 year	938 per 1000	**788 per 1000** (675 to 928)	**RR 0.84** (0.72 to 0.99)	96 (1 RCT)	⊕⊕◯◯ Low[a,b]	—
Incidence of SAEs	21 per 1000	**21 per 1000** (1 to 257)	**POR 1.00** (0.06 to 16.22)	96 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	—
All-cause mortality - at 1 year - trial end	0 per 1000	**0 per 1000** (0 to 0)	**RD 0.00** (-0.04 to 0.04)	96 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	No deaths occurred during the trial period, though the sample size was significantly below the optimal information size to make any assessment of risk.
Sustained adherence	See comments.			—	—	Sustained adherence is reported as adherence since the trial was 1 year in duration and end of trial adherence data were reported.
QoL	See comments.			96 (1 RCT)	—	1 RCT used SF-36 to measure QoL; the results are presented as a bar graph only, with mean and SD not re-

ported in extractable form (Elalfy 2015). Stated no difference between groups.

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **DFP**: deferiprone; **DFX**: deferasirox; **POR**: Peto odds ratio; **QoL**: quality of life; **RCT**: randomised controlled trial; **RD:** risk difference; **RR:** risk ratio; **SAE**: serious adverse event

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
[a]We downgraded the certainty of evidence once for risk of bias as there was high or unclear risk of bias in three domains.
[b]We downgraded the certainty of evidence once for indirectness as the trial included children aged 10 to 18 years with severe iron overload.
[c]We downgraded the certainty of evidence once for imprecision as the comparison has wide CIs.
[d]Downgraded twice for imprecision due to the small sample size, far below the optimal information size for mortality.

Summary of findings 8. Summary of findings: Comparison 8 - medication management versus standard care

Intervention: medication management

Comparison: standard care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	Risk with medication management				
Adherence to iron chelation	See comments.		—	—	—	This outcome was not reported in the control group and therefore there are no comparative data.
SAEs	Outcome not reported.			—	—	—
Mortality	Outcome not reported.			—	—	—
Sustained adherence	Outcome not reported.			—	—	—

QoL PedsQLTM total score Follow-up: 6 months	See comments.	—	48 (1 RCT)	⊕◯◯◯ Very low[a,b]	1 RCT reported medians and IQRs. Medication management: 63.51 (51.75 to 84.54), n = 24; standard care: 49.84 (41.9 to 60.81), n = 24.

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **IQR**: interquartile range; **PedsQLTM**: Pediatric Quality of Life InventoryTM: **QoL**: quality of life; **RCT**: randomised controlled trial; **SAE**: serious adverse event

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
[a]We downgraded the certainty of evidence twice for risk of bias due to high or uncertain risk of bias in all domains.
[b]We downgraded the certainty of evidence twice for indirectness because most outcomes were only reported in the medication management group.

BACKGROUND

Description of the condition

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

Sickle cell disease

SCD is an inheritable blood disorder, which can lead to life-threatening complications. People with SCD experience episodes of severe pain and other complications including anaemia, end-organ damage, pulmonary complications, kidney disease, and increased susceptibility to infections and stroke (Pleasants 2014). It is one of the most common severe monogenic disorders in the world, due to the inheritance of two abnormal haemoglobin (beta globin) genes (Rees 2010). Populations originating from sub-Saharan Africa, Spanish-speaking regions in the western hemisphere (South America, the Caribbean and Central America), the Middle East, India and parts of the Mediterranean are predominantly affected. Reductions in infant and child mortality and increasing migration from highly affected countries have made this a worldwide problem (Piel 2012). Over 12,500 people in the UK and 100,000 in the USA suffer from the disease (NICE 2010; Pleasants 2014).

The term SCD refers to all mutations that cause the disease, of which there are three main types. Sickle cell anaemia is the most common form of the disease (up to 70% of cases of SCD in people of African origin) and is due to the inheritance of two beta globin S (βS) alleles (haemoglobin (Hb)SS). The second most common genotype (up to 30% of cases in people of African origin) is haemoglobin SC disease (HbSC disease) and is due to the co-inheritance of the βS and βC alleles; this tends to be a more moderate form of the disease. The third major type of SCD occurs when βS is inherited with a β-thalassaemia allele, causing HbS/β-thalassaemia (Rees 2010). People who have inherited a thalassaemia null mutation (HbSβ^{o}) have a disease that is clinically indistinguishable from sickle cell anaemia, whereas people with HbSβ^{+} thalassaemia have a milder disorder. In high-income nations, people with SCD are expected to live into their 40s, 50s and beyond; whereas in low-income countries, including some African nations, it is estimated that between 50% to 90% of children born with HbSS die before their fifth birthday (Gravitz 2014; Grosse 2011).

Red blood cell transfusions can be given to treat complications of SCD (e.g. acute chest syndrome); this often involves a single transfusion episode, or they can be part of a regular long-term transfusion programme to prevent complications of SCD such as stroke in children (Yawn 2014).

Thalassaemia

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

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

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

Iron chelation therapy and adherence

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

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

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

Adherence to medications is defined as the extent to which a person's use of the medicine matches the agreed prescription from the healthcare provider (NICE 2009; Walsh 2014). Moderate adherence is defined as taking 60% to 80% of a prescribed dose, while high adherence can include the continued use of the medicine or taking at least 80% of the recommended dose. There are several ways to measure adherence including the self-reporting of medication use or more objective factors such as pill counts, prescription refills, urinary assays or, in the case of iron chelation, signs of iron overload (Ryan 2014; Walsh 2014). Adherence rates can vary widely; a recent review reported that adherence rates to DFX ranged between 22% and 89% (Loiselle 2016).

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

Description of the intervention

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

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

Psychological and psychosocial interventions

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

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

Education interventions

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

Medication interventions

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

How the intervention might work

Psychological and psychosocial interventions

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

Educational interventions

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

Medication interventions

Iron levels are monitored in people receiving regular transfusions. An increasing iron burden may necessitate medication changes or

more aggressive iron chelation therapy such as increasing doses or combination therapy. People may also change medications multiple times due to worsening iron overload, side effects or personal preferences (Trachtenberg 2014). Medication changes that reflect personal preferences or minimise harms and improve outcomes, combined with medication reconciliation strategies including audit and feedback, prescription and medication help lines, counselling and age-appropriate discharge instructions, may help to address and improve adherence (NCCPC 2009; Ryan 2014). Medication interventions also include medication management which is a person-centred intervention by a clinician (often a pharmacist) to optimise drug therapy in order to improve outcomes for the person (American Pharmacists Association 2008).

Why it is important to do this review

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

This is an update of the review, last published in 2018 (Fortin 2018).

OBJECTIVES

To identify and assess the effectiveness of different types of interventions (psychological and psychosocial, educational, medication interventions, or multi-component interventions) and interventions specific to different age groups, to improve adherence to iron chelation therapy compared to another listed intervention, or standard care in people with SCD or thalassaemia.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) comparing one or more adherence interventions to another listed intervention, or standard care.

For studies comparing medications or medication changes, we only included RCTs (as per our protocol).

As per our protocol, for studies including psychological and psychosocial interventions, educational interventions, or multi-component interventions, we also planned to include non-randomised studies of interventions (NRSIs), controlled before-after (CBA) studies and interrupted time series (ITS) studies including repeated measures designs, which we have done for the 2022 update. We used the Cochrane Effective Practice and Organisation of Care (EPOC) Group's definition of study designs to consider studies for inclusion (EPOC 2015).

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

We planned to include ITS and repeated measures studies that had a clearly defined point in time when the intervention occurred and at least three data points before and after the intervention. We excluded ITS studies that did not have a clearly defined point in time when the intervention occurred, or fewer than three data points before and after the intervention, or the ITS study ignored secular (trend) changes, performed a simple t-test of the pre- versus post-intervention periods and re-analysis of the data was not possible (in accordance with EPOC 2015 recommendations).

Types of participants

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

Types of interventions

We planned to compare the active interventions listed below to each other or to standard care (as defined in the trial).

1. Psychological and psychosocial Interventions
2. Educational interventions
3. Medication interventions
4. Multi-component interventions (combining aspects of the above interventions)

Types of outcome measures

We planned to assess the following outcome measures.

Primary outcomes

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

We categorised all-cause mortality and SAEs according to short-, medium- and long-term outcomes. We reported the exact definition of these time frames over time periods that are common to as many trials as possible (e.g. zero to one year, one to five years, over five years).

Secondary outcomes

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

We categorised health-related QoL, iron overload and organ damage according to short-, medium- and long-term outcomes. We reported the exact definition of these time frames over time periods that are common to as many studies as possible (e.g. up to six months, six to 12 months, over 12 months).

Search methods for identification of studies

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

Electronic searches

We identified studies from the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register using the terms: (sickle cell OR thalassaemia OR (haemoglobinopathies AND general)) AND iron chelation.

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the *Cochrane Library*) and weekly searches of MEDLINE. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Public Health Agency Annual Scientific Meeting (formerly the Caribbean Health Research Council Meeting); and the National Sickle Cell Disease Program Annual Meeting. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

Date of the most recent search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register: 1 August 2022.

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

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 12, the *Cochrane Library*) (www.cochranelibrary.com/) searched on 13 December 2021;
2. PubMed (Epub Ahead of Print, In-Process and Other Non-Indexed Citations, for recent records not yet added to MEDLINE) (www.ncbi.nlm.nih.gov/sites/entrez) searched on 13 December 2021;
3. MEDLINE (Ovid, ALL, 1946 to 13 December 2021);
4. Embase (OvidSP, 1974 to 13 December 2021);
5. CINAHL (EBSCOHost, 1937 to 13 December 2021);
6. APA PsycINFO (Ovid, 1967 to 13 December 2021);
7. ProQuest Dissertations & Theses Global (ProQuest, 1861 to 13 December 2021);
8. Web of Science & Social Sciences Conference Proceedings Indexes (CPSI-S & CPSSI, Clarivate, 1990 to 13 December 2021).

We also searched the following trial registries for ongoing trials:

1. ClinicalTrials.gov (clinicaltrials.gov/) searched on 13 December 2021;
2. WHO International Clinical Trials Registry Platform (ICTRP) (trialsearch.who.int/) searched on 13 December 2021;
3. International Standard Randomised Controlled Trial Number (ISRCTN) registry (www.isrctn.com/) searched on 13 December 2021.

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

Please note: we previously searched the Psychology and Behavioral Sciences Collection (last searched 1 February 2017), but no longer have access to this resource.

Searching other resources

We hand searched the reference lists of included trials in order to identify further relevant trials.

Data collection and analysis

Selection of studies

We selected trials according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2022). For the 2022 update, two authors (LJG, LE) independently screened all electronically derived citations and abstracts of papers identified by the search strategy for relevance. We excluded studies that were clearly irrelevant at this stage based on the abstract. The same review authors (LJG, LE) independently assessed the full texts of all potentially relevant studies for eligibility against the criteria outlined above. We resolved disagreements by discussion.

We sought further information from trial investigators if the trial report or abstract contained insufficient data to make a decision about eligibility. We used Covidence software to assess trial eligibility, which included ascertaining whether the participants had SCD or thalassaemia, if the trial addressed interventions to improve adherence to iron chelation therapy, and whether the trial was randomised or a NRSI or a CBA or an ITS study (Covidence). We recorded the reasons why potentially relevant studies failed to meet the eligibility criteria.

Data extraction and management

For the 2022 update, two review authors (LJG, LE) extracted the data according to Cochrane guidelines (Li 2022). We resolved disagreements by consensus. We extracted data independently for all of the trials using Covidence modified to reflect the outcomes in this review (Covidence). In addition, we used the available tables in Review Manager 5 to extract data on trial characteristics as below (RevMan 2014).

General information

Review author's name, date of data extraction, study ID, first author of study, author's contact address (if available), citation of paper, objectives of the study.

Study details

Design, location, setting, sample size, power calculation, treatment allocation, inclusion and exclusion criteria, reasons for exclusion, comparability of groups, length of follow-up, stratification, stopping rules described, statistical analysis, results, conclusion and funding.

Characteristics of participants

Age, gender, total number recruited, total number randomised, total number analysed, types of underlying disease, loss to follow-

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

Interventions

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

Outcomes measured

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

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

For the current update, two review authors (LJG, LE) entered data into RevManWeb, and we resolved disagreements by consensus.

If we had identified NRSIs, we planned to extract data according to the criteria developed for NRSIs as recommended in the *Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2022). In addition to the items above, for NRSIs, CBA and ITS studies, we also planned to collect data on: confounding factors; the comparability of groups on confounding factors; methods used to control for confounding and on multiple effect estimates (both unadjusted and adjusted estimates) as recommended in the *Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2022).

Assessment of risk of bias in included studies

For the 2022 update, two review authors (LJG, LE) assessed all included trials for possible risks of bias as described in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2017).

The assessment included information about the design, the conduct and the analysis of the trial. We assessed each criterion using the Cochrane tool for assessing the risk of bias for RCTs (classed as 'low', 'high' or 'unclear' risk) in the following areas:

1. Selection bias (random sequence generation and allocation concealment)
2. Performance bias (blinding of participants and personnel)
3. Detection bias (blinding of outcome assessment)
4. Attrition bias (incomplete outcome data)
5. Reporting bias (selective reporting)
6. Other bias

We resolved disagreements on the assessment of quality of an included trial by discussion until we reached consensus.

Most included trials were RCTs. For the one NRSI, we used the ROBINS-I tool (Risk Of Bias In Non-randomized Studies of Interventions), which would be used to rate the quality of other NRSIs and CBA studies in future updates (Sterne 2016). The tool uses signalling questions and covers seven domains (listed below) where the quality of evidence is rated as 'low', 'moderate', 'serious', 'critical' or 'no information'. Please refer to an appendix for a copy of the tool (Appendix 2).

1. Bias due to confounding
2. Bias in the selection of participants
3. Bias in measurement of interventions
4. Bias due to departure from intended interventions
5. Bias due to missing data
6. Bias in measurement of outcomes
7. Bias in the selection of the reported result

In future updates of this review, for ITS studies we plan to use the risk of bias criteria below as suggested for EPOC reviews (EPOC 2015).

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

Measures of treatment effect

RCTs

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

For RCTs of dichotomous outcomes we recorded the number of events and the total number of participants in both the treatment and control groups and reported the pooled risk ratio (RR) with a 95% CI (Deeks 2022). Where the number of observed events is small (less than 5% of sample per group), and where trials have balanced treatment groups, we have reported the Peto odds ratio (OR) with 95% CI (Deeks 2022). Where there were zero cases in both arms, we have reported risk difference (RD) with 95% CI.

Where adverse events (AEs) or serious adverse events (SAEs) (including organ damage) have been reported as individual categories, and were not available as a total number, we have used 99% CIs to avoid giving undue weight to multiple analyses, as described in the *Cochrane Handbook for Systematic Reviews of Interventions*.

There were no eligible cluster-randomised trials. If such trials are included in future updates of this review, we plan to extract and report direct estimates of the effect measure (e.g. RR with a 95% CI) from an analysis that accounts for the clustered design. We will obtain statistical advice to ensure the analysis is appropriate. If appropriate analyses are not available, we will make every effort to approximate the analysis following the recommendations in

chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022).

Non-randomised studies

We identified one non-randomised study of an intervention (NRSI), although the data could not be used due to severe baseline confounding. If we include such studies with usable data in future updates of this review, we plan to extract and report the RR with a 95% CI for dichotomous outcomes, adjusting for baseline differences (such as Poisson regressions or logistic regressions) or the ratio of RRs (i.e. the RR post intervention/RR pre intervention).

For continuous variables we will extract and report the absolute change from a statistical analysis adjusting for baseline differences (e.g. regression models, mixed models or hierarchical models) or the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute post-intervention difference between the intervention and control groups, as well as the absolute pre-intervention difference between the intervention and control groups/the post-intervention level in the control group) (EPOC 2015).

ITS studies

There were no eligible ITS studies. If we include such studies in future updates, we plan to standardise data by dividing the level (or time slope) and standard error (SE) by the SD of the pre-intervention slope, in order to obtain the effect sizes.

Where appropriate, we plan to report the number needed to treat to benefit (NNTB) and the number needed to treat to harm (NNTH) with CIs.

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

Unit of analysis issues

For trials with multiple treatment groups or interventions, we included subgroups that we considered relevant to the analysis. If appropriate, we combined groups to create a single pair-wise comparison. If this was not possible, we selected the most appropriate pair of interventions and excluded the others (Higgins 2022). No trials randomised participants more than once.

There were no included cluster-randomised studies or NRSIs. If we include these in future updates of this review, we plan to treat any unit of analysis issues that arise in accordance with the advice given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022).

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

Dealing with missing data

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

We recorded the number of participants lost to follow-up for each trial. Where possible, we analysed data on an intention-to-treat (ITT) basis, but if insufficient data were available, we also presented a per protocol analyses (Higgins 2017).

Assessment of heterogeneity

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

We assessed statistical heterogeneity of treatment effects between trials using a Chi^2 test with a significance level at $P < 0.1$. We used the I^2 statistic to quantify the degree of potential heterogeneity and classified it as moderate if the I^2 was greater than 50%, or considerable if I^2 was greater than 75%. We used the random-effects model as we anticipated that we would identify at least moderate clinical and methodological heterogeneity within the trials selected for inclusion. If statistical heterogeneity was considerable, we did not report the overall summary statistic. We assessed potential causes of heterogeneity by sensitivity and subgroup analyses (Deeks 2022).

Assessment of reporting biases

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

Data synthesis

If trials were sufficiently homogenous in their design, we conducted a meta-analysis according to the recommendations of Cochrane (Deeks 2022). We used the random-effects model for all analyses as we anticipated that true effects would be related but not the same for included trials. If we could not perform a meta-analysis we commented on the results as a narrative.

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

If identified, we planned to analyse NRSIs or CBA studies separately. We planned to analyse outcomes with adjusted effect estimates if these were adjusted for the same factors using the inverse variance method as recommended in the *Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2022). For ITS studies, we would have used the effect sizes (if reported in the included studies or obtained (as described earlier)) and pooled them using the generic inverse variance method in Review Manager 5 (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

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

There were insufficient data to perform some of the planned subgroup analyses. We planned to perform subgroup analyses according to Cochrane's recommendations (Deeks 2022) for each of the following criteria, and separately for the different study design types included in the review in order to assess the effect on heterogeneity.

1. Age of participant: child (one to 12 years), adolescent (13 to 17 years), adult (18+ years)
2. Route of administration of iron chelating agents: oral, intravenous or subcutaneous

Sensitivity analysis

There were insufficient data to perform the planned sensitivity analyses. If we had obtained adequate data, we planned to assess the robustness of our findings by performing the following sensitivity analyses according to Cochrane recommendations where appropriate (Deeks 2022).

1. Including only those trials with a 'low' risk of bias (e.g. RCTs with methods assessed as low risk for random sequence generation and concealment of treatment allocation)
2. Including only those studies with less than a 20% dropout rate
3. Duration of follow-up (up to and including six months compared to over six months)

Summary of findings and assessment of the certainty of the evidence

We assessed the certainty of evidence using GRADEpro software, and exported this as summary of findings tables.

We used the GRADE approach to generate a summary of findings table for each comparison we present in the review, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022). We rated the certainty of the evidence as 'high', 'moderate', 'low' or 'very low' using the five GRADE considerations.

1. Risk of bias (serious or very serious)
2. Inconsistency (serious or very serious)
3. Indirectness (serious or very serious)
4. Imprecision (serious or very serious)
5. Publication bias (likely or very likely)

For NRSIs or CBA or ITS studies, we planned to consider the following factors.

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

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

Within each summary of findings table, we have presented our listed outcomes of:

1. adherence rates (minimum of three months);
2. SAEs (most common time frame used in most studies);
3. all-cause mortality (most common time frame used in most studies);
4. sustained adherence (six months or more); and
5. QoL (most common time frame used in most studies).

Where analysis was not possible, we have described the data narratively, or stated not reported.

RESULTS

Description of studies

See also Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

See PRISMA flow diagram for details of this review update (Figure 1).

Figure 1. CFGD trials register: Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register

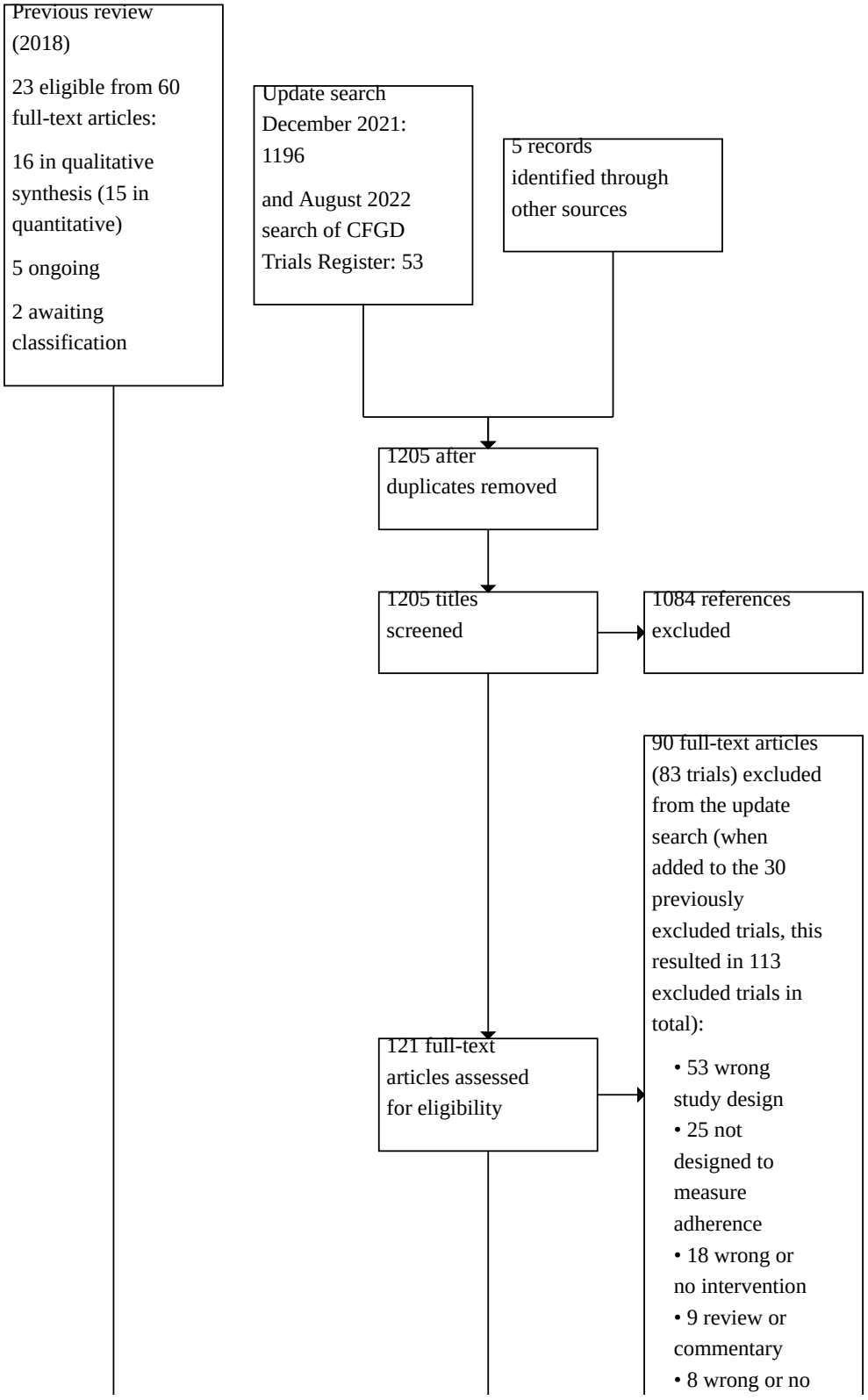


Figure 1. (Continued)

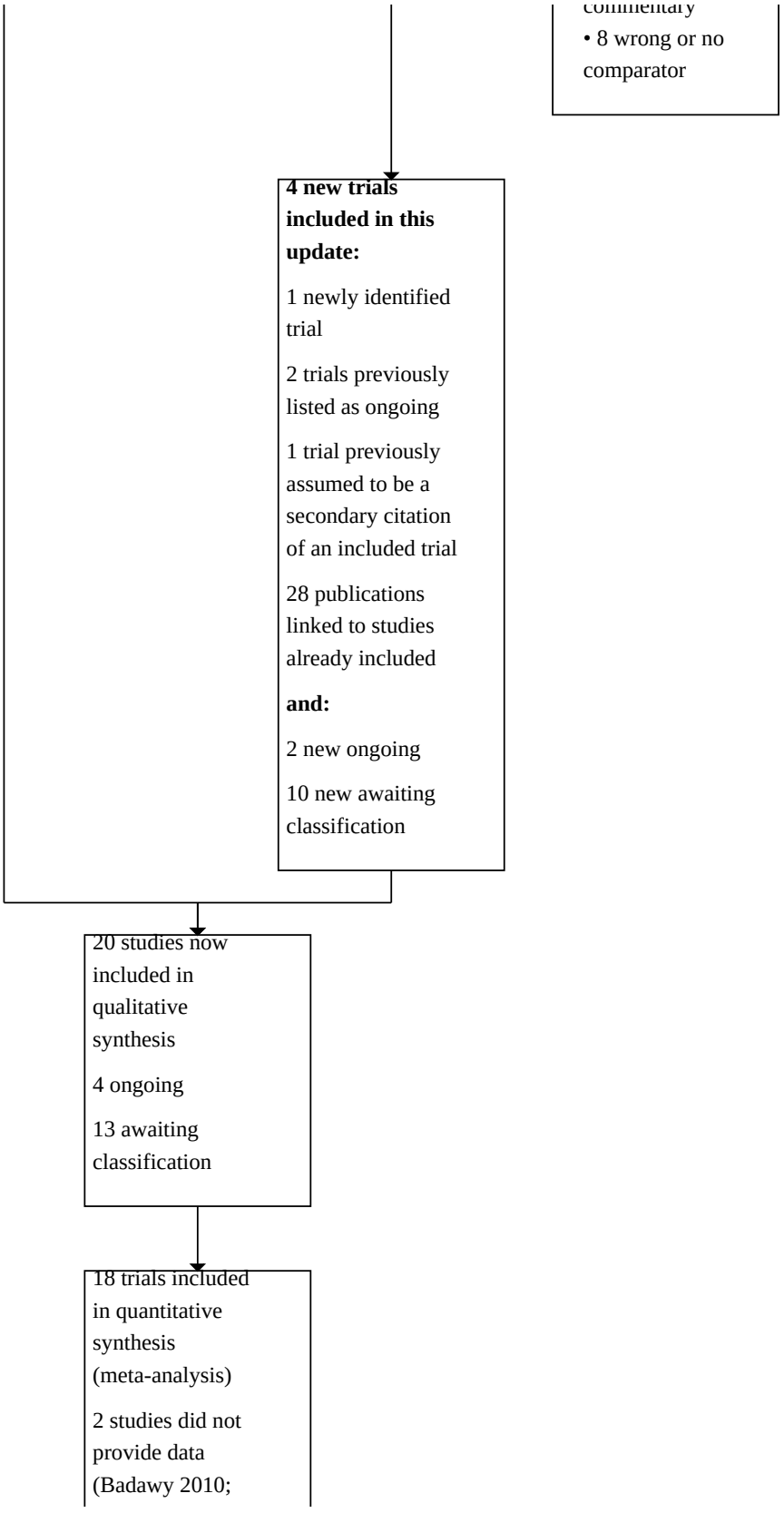


Figure 1. (Continued)

provide data
(Badawy 2010;
Gharaati 2019)

In the 2022 update searches for this review we identified a total of 1254 potentially relevant references (1249 through electronic searching and five identified though other sources). After removing duplicates, there were 1205 references, of which two review authors (LJG, LE) excluded 1084 references on the basis of the abstract. The review authors then reviewed 121 full-text articles for relevance and excluded a further 90 references (equating to 83 trials) (see Characteristics of excluded studies for reasons).

Forty-one references were included and assigned as: one new trial, two newly ongoing, 10 newly awaiting classification, 28 newly identified references that were linked to studies already included, which we checked for additional data, and one reference previously assumed to be a secondary citation of an included trial that was separately included.

We re-assessed those previously listed as ongoing or awaiting classification, to ascertain whether or not they should be included.

In this update we included four new trials: one newly identified non-randomised trial (Gharaati 2019), two trials previously listed as ongoing (Kwiatkowski 2021; Maggio 2020), and one trial (Calvaruso 2014) that had been incorrectly merged with another (Calvaruso 2015) due to misreporting of trial registration numbers within the publications. We also identified two new ongoing trials, and 10 new trials are awaiting classification.

Combined with the previous review, this resulted in 20 trials being included in the qualitative synthesis (four are listed as ongoing and 13 are awaiting classification), of which we have included 18 trials in the quantitative analysis, as two studies did not provide sufficient usable data (Badawy 2010; Gharaati 2019).

Included studies

Nineteen RCTs and one NRSI (Gharaati 2019) met the pre-defined inclusion criteria (Aydinok 2007; Badawy 2010; Bahnasawy 2017; Calvaruso 2014; Calvaruso 2015; Elalfy 2015; El Beshlawy 2008; Galanello 2006a; Hassan 2016; Kwiatkowski 2021; Mourad 2003; Olivieri 1997; Pennell 2006; Pennell 2014; Taher 2017; Tanner 2007; Vichinsky 2007).

Two of the included trials were abstract reports only (Badawy 2010; Olivieri 1997). One abstract did not report outcomes by intervention and therefore was not included in the quantitative reporting of the effects of interventions (Badawy 2010). One NRSI was not included in the quantitative analyses due to severe baseline confounding (Gharaati 2019).

Trial design

There were 18 RCTs of medication interventions (Aydinok 2007; Badawy 2010; Calvaruso 2014; Calvaruso 2015; Elalfy 2015; El Beshlawy 2008; Galanello 2006a; Hassan 2016; Kwiatkowski 2021; Mourad 2003; Olivieri 1997; Pennell 2006; Pennell 2014; Taher 2017; Tanner 2007; Vichinsky 2007), one RCT on medication management (Bahnasawy 2017), and one quasi-experimental trial (a NRSI) on education (Gharaati 2019).

We included 13 multicentre trials (Calvaruso 2014; Calvaruso 2015; Elalfy 2015; Galanello 2006a; Kwiatkowski 2021; Maggio 2009;Maggio 2020; Olivieri 1997; Pennell 2006; Pennell 2014; Taher 2017; Tanner 2007; Vichinsky 2007), which ranged from two centres in one country (Calvaruso 2015; Elalfy 2015; Olivieri 1997) to 44 centres in multiple countries (Vichinsky 2007). Seven were single-centre trials (Aydinok 2007; Bahnasawy 2017; Badawy 2010; El Beshlawy 2008; Gharaati 2019; Hassan 2016; Mourad 2003).

Follow-up ranged from six months in two trials (Bahnasawy 2017; Taher 2017) to five years (Calvaruso 2014; Maggio 2009), with a 10-year follow-up for some outcomes (Calvaruso 2015). The remainder of the trials were of 12 months duration, except Olivieri 1997, which had 24 months follow-up; one trial did not report follow-up time (Badawy 2010).

One trial was terminated early; this was a sponsor decision due to issues of recruitment: the pool of potential patients was exhausted, and sufficient information had already been obtained (Kwiatkowski 2021).

Trial size

The number of participants enrolled in the trials ranged from 24 (Aydinok 2007) to 390 (Maggio 2020). Sample size calculations were reported in eight trials (Calvaruso 2015; Elalfy 2015; El Beshlawy 2008; Maggio 2009; Pennell 2006; Pennell 2014; Tanner 2007; Vichinsky 2007).

Setting

Trials were published between 1997 and 2021. Five were conducted in Egypt (Badawy 2010; Bahnasawy 2017; Elalfy 2015; El Beshlawy 2008, Hassan 2016); six in Italy (Calvaruso 2014; Calvaruso 2015; Galanello 2006a; Maggio 2009; Pennell 2006; Tanner 2007); and five were international multicentre trials conducted in several countries (Kwiatkowski 2021; Maggio 2020; Pennell 2014; Taher 2017; Vichinsky 2007). One trial was conducted in each of the following countries: Turkey (Aydinok 2007); Lebanon (Mourad 2003); Iran (Gharaati 2019); and Canada (Olivieri 1997).

Participants

A total of 14 trials included only participants with β-thalassaemia major (Aydinok 2007; Badawy 2010; Bahnasawy 2017; Elalfy 2015; El Beshlawy 2008; Galanello 2006a; Gharaati 2019; Hassan 2016; Maggio 2009; Mourad 2003; Olivieri 1997; Pennell 2006; Pennell 2014; Tanner 2007); one trial included only participants with thalassaemia intermedia (Calvaruso 2015); and two trials included

only participants with SCD (Calvaruso 2014; Vichinsky 2007). Three trials included a mixture of participants: one trial assessed SCD or "other iron overload", excluding thalassaemia (Kwiatkowski 2021), one included thalassaemia or "other iron overload" (Taher 2017), and one included "any hereditary haemoglobinopathy (including SCD or thalassaemia)" (Maggio 2020).

The mean age ranged from 11 years (El Beshlawy 2008) to 41 years (Calvaruso 2015). One trial reported the proportion of participants falling into different age categories (< 6 years old, approximately 30%; 6 to 10 years, approximately 25%, > 10 years, approximately 45%) (Maggio 2020). Two trials only provided the minimum age of enrolment into the RCT: at least eight years old in Badawy 2010 and at least 10 years old in Olivieri 1997.

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

Intervention

In this review we report the Effects of interventions by the various comparisons in the different trials. Most trials assessed medication interventions, but one trial assessed a medication management intervention by a clinical pharmacist (Bahnasawy 2017), and a further (non-randomised) trial assessed a phone-mediated educational intervention about the condition and treatment (Gharaati 2019).

The comparisons and studies included:

1. **DFP versus DFO**: seven trials (Badawy 2010; Calvaruso 2014; Kwiatkowski 2021; Calvaruso 2015; El Beshlawy 2008; Olivieri 1997; Pennell 2006); see Table 2.
2. **DFX versus DFO**: three trials (Hassan 2016; Pennell 2014; Vichinsky 2007); see Table 3.
3. **DFP versus DFX**: one trial (Maggio 2020); see Table 4.
4. **DFX (film-coated tablet (FCT) versus DFX (dispersible tablet (DT)))**: one trial (Taher 2017); see Table 5.
5. **DFP and DFO combined versus DFP alone**: four trials (Aydinok 2007; Badawy 2010; El Beshlawy 2008; Maggio 2009); see Table 6.
6. **DFP and DFO combined versus DFO alone**: five trials (Badawy 2010; El Beshlawy 2008; Galanello 2006a; Mourad 2003; Tanner 2007); see Table 7.
7. **DFP and DFO combined versus DFP and DFX combined**: one trial (Elalfy 2015); see Table 8.
8. **Medication management versus standard care**: one trial (Bahnasawy 2017); see Table 9.
9. **Education versus standard care**: one non-randomised trial (Gharaati 2019); see Table 10.

Outcomes

Outcomes varied across trials depending on the objectives. All trials measured adherence (Table 1), although this was usually as a secondary rather than a primary outcome. Reduction in serum ferritin or liver iron concentration (LIC) were the primary outcomes in most trials; however, in three trials the primary outcome was myocardial T2* MRI results (Pennell 2006; Pennell 2014; Tanner 2007) and in one trial was overall safety (Taher 2017). Safety (including both SAEs and AEs) was included as a secondary outcome in all trials. Four trials reported on QoL (Aydinok 2007; Bahnasawy 2017; Elalfy 2015; Kwiatkowski 2021).

Source

Seven trials identified non-profit organisations, including universities, foundations and societies, as their source of support (Badawy 2010; Calvaruso 2014; Calvaruso 2015; Elalfy 2015; Gharaati 2019; Maggio 2009; Maggio 2020).

Six trials identified industry sponsorships (Galanello 2006a; Kwiatkowski 2021; Pennell 2006; Pennell 2014; Taher 2017; Vichinsky 2007). Six trials did not state their source of funding (Aydinok 2007; Bahnasawy 2017; El Beshlawy 2008; Hassan 2016; Mourad 2003; Olivieri 1997), but of these, three may have had industry funding. In one trial, drugs were supplied by the manufacturer (Aydinok 2007), one trial was halted by the manufacturer (Olivieri 1997) and one trial included industry employees as authors (El Beshlawy 2008).

One trial had a mix of non-profit and industry funding (Tanner 2007).

Excluded studies

We excluded a total of 113 trials:

- 53 studies had the wrong study design (e.g. non RCT for a medication review) (Abu 2015; Aftab 2017; Al Kloub 2014; Al Kloub 2014a; Al Refaie 1995; Allemang 2016; Alvarez 2009; Anderson 2017; Anderson 2018; Angelucci 2005; Ansari 2017; Arian 2018; Bartin Gooden 2015; Bazpour 2019; Biabani 2020; Canatan 2004; Cappellini 2005b; Cappellini 2017; Cheesman 2018; Daar 2010; Deugnier 2005; Deugnier 2010; Ding 2017; Elalfy 2016; Elalfy 2018; Eshghi 2018; EUCTR 2007-000766-20-IT; Farhady 2020; Galanello 2006b; Gallo 2014; Gordon 2018; Inusa 2022; IRCT 2015 012914504N3; IRCT 2017 0512033932N5; Kattamis 2021; Kidson Gerber 2008; Kolnagou 2008; Mohamed Al Nasiri 2018; NCT03233269; NCT03591575; NCT03637556; NCT04092205; Pantalone 2011a; Porter 2012; Safaei 2019; Sanjeeva 2015; Shah 2021; Smith 2017; Tripathy 2021; UMIN 000007644; Viola 2020; Vlachodimitropoulou Koumoutsea 2017; Wilson 2017);
- 25 studies were not designed to measure adherence (Bellanti 2017; Bellanti 2017a; Berkovitch 1995; Bin Ahmed 2018; Chakrabarti 2013; Habibian 2014; IRCT 2009 0813002342N9 (Rafati 2022); IRCT 2016 041627412N1; IRCT 2018 0207038655N1; Jhinger 2018; Kompany 2009; Madmoli 2019; Matti 2013; Molavi 2013; Molavi 2014; Molazem 2016; NCT00061750; NCT01709032; NCT03381833; Peng 2013; Sebastian 2020; Souran 2019; Vichinsky 2008; Waheed 2014; Yarali 2006);
- 18 studies either had no intervention or the wrong intervention (Adibi 2012; Al-Momen 2020; Armstrong 2011; Aydinok 2016; Bala 2014; Belgrave 1989; Darvishi-Khezri 2017; EUCTR 2015-003225-33-GR; Gomber 2004; Hagag 2013; Hamed 2020; Kejriwal 2020; Mohammadi 2018; NCT03342404; NCT04292314; NCT04541875; NCT04688411; Sidhu 2021);
- nine studies were a review or a commentary (Chaudhary 2021; Emami Zeydi 2018; Hankins 2020; Hankins 2021; Kattamis 2018; Loiselle 2015; Loiselle 2016; Shih 2020; Walsh 2014); and
- eight studies either had no comparator or the wrong comparison (Aziz 2021; EUCTR 2007-004008-10; Leonard 2014;

Mazzone 2009; NCT02133560; NCT02466555; Pakbaz 2005; Patalia Abishek 2014).

Studies awaiting classification

We assessed 13 trials as awaiting classification: seven are RCTs assessing medication interventions (Bhojak 2020; CTRI/2020/07/026771; EUCTR 2017-003777-34-NL; Eghbali 2019; IRCT 2016 0310026998N7; IRCT 2019 0106042262N1; NCT00004982); six are non-medical interventions, including various forms of education (EX-PAT 2013; IRCT 2013 042213092N1; IRCT 2020 0606047670N2021), psycho-education (IRCT 2019 0827044634N1; IRCT 2020 0126046270N1), or monitoring (Crosby 2019) compared to standard care. See Table 11 for an overview of studies awaiting classification, including individual reasons for their classification, and Characteristics of studies awaiting classification for more detail.

Ongoing studies

We identified four ongoing trials: two RCTs assessing medication interventions (CALYPSO; IRCT 2015 101218603N2), one RCT of group versus individual appointments (Madderom 2016 (TEAM study)), and one RCT of repeated psycho-medical education compared to a single education session (NCT04877054). See Table 12 for an overview of ongoing studies, and Ongoing studies for more detail.

Risk of bias in included studies

Please refer to the figures section of the review for visual representations of the assessments of risk of bias across all trials and for each item in the included trials (Figure 2; Figure 3). Please also see the risk of bias section in the Characteristics of included studies section for further information about the bias identified within individual trials.

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

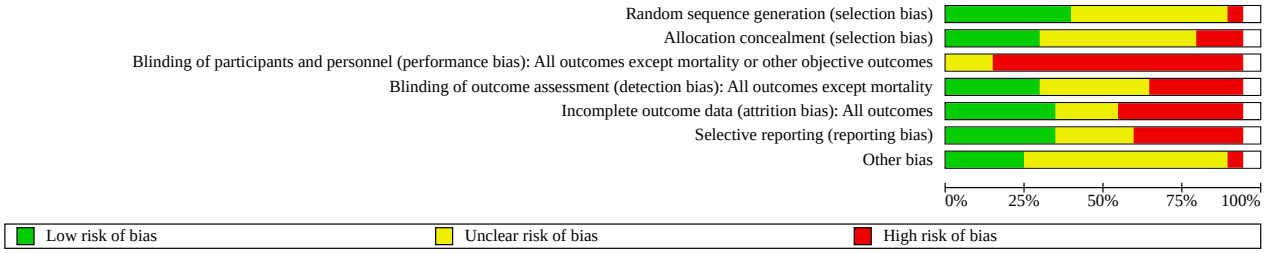


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

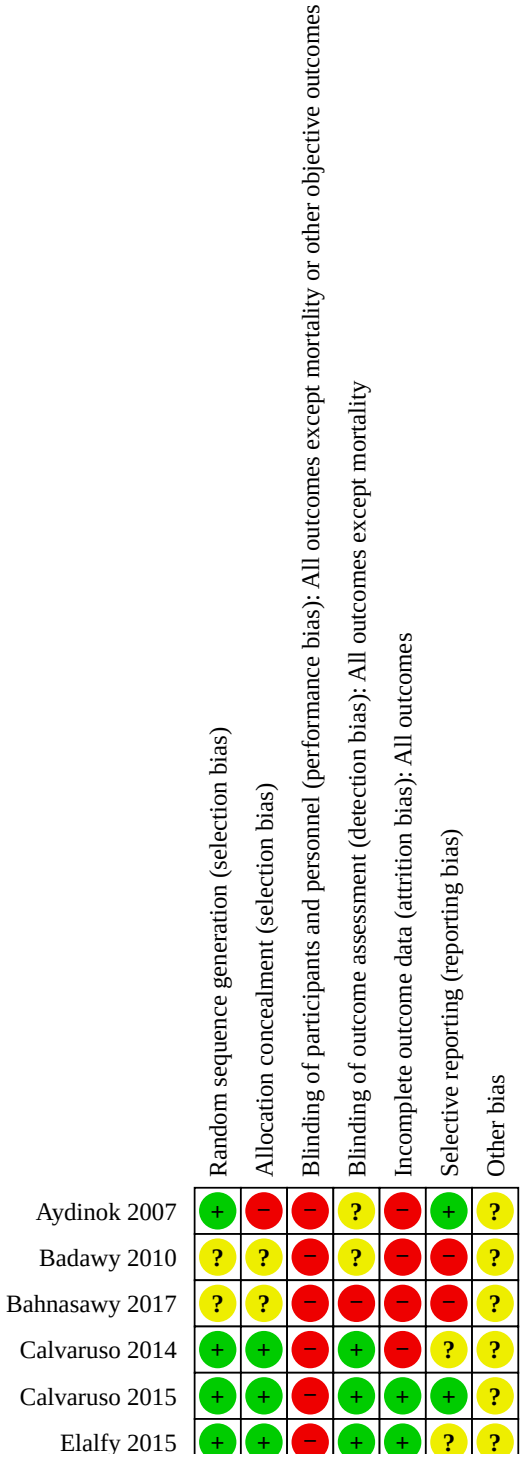
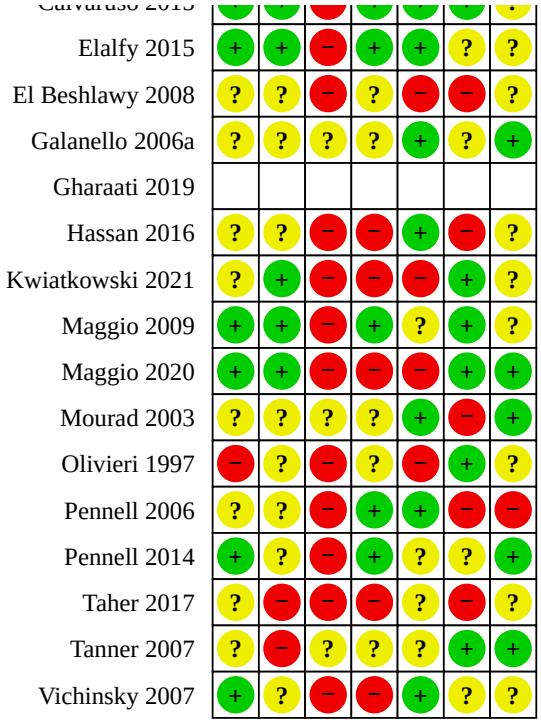


Figure 3. (Continued)



One NRSI was assessed using ROBINS-I (Gharaati 2019) (Appendix 2); we judged this as having a critical risk of bias due to severe baseline confounding (domain 1.4, baseline imbalance that was not accounted for, or noted within their publication) in important assessments that may affect our outcomes (baseline knowledge, attitude and performance; and previous medical history). Due to the early note of severe confounding, we then stopped the risk of bias assessment and were unable to use the extracted data in any analyses.

Allocation

Random sequence generation

We considered eight trials to be at a low risk of bias for random sequence generation as randomisation was clearly described and done centrally, in permuted blocks, or computer-generated (Aydinok 2007; Calvaruso 2015; Calvaruso 2014; Elalfy 2015; Maggio 2009; Maggio 2020; Pennell 2014; Vichinsky 2007).

We considered 10 trials to be at an unclear risk of bias. Although one trial used permuted blocks there were several imbalances in baseline characteristics between groups (Hassan 2016). We judged the remaining nine trials to have an unclear risk of bias as there was no description of randomisation and the report only stated that participants were randomised (Badawy 2010; Bahnasawy 2017; El Beshlawy 2008; Galanello 2006a; Kwiatkowski 2021; Mourad 2003; Pennell 2006; Taher 2017; Tanner 2007).

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

Allocation concealment (selection bias)

We considered six trials to be at low risk for selection bias as participants were allocated by telephone contact from a co-ordinating centre (Calvaruso 2014; Calvaruso 2015; Elalfy 2015; Kwiatkowski 2021; Maggio 2009; Maggio 2020).

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

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

Blinding

Blinding of participants and personnel (performance bias)

No trials were able to blind the participants or personnel to group allocation, and so could not be considered at low risk of bias (except for measures of mortality as this is unlikely to be affected by knowledge of treatment).

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

We considered 16 trials to be at a high risk for performance bias. Trials were either open-label, did not mention blinding, or blinding was difficult due to type of treatment: a subcutaneous injection compared to an oral intervention or combination of both (Aydinok 2007; Badawy 2010; Bahnasawy 2017; El Beshlawy 2008; Calvaruso 2014; Calvaruso 2015; Elalfy 2015; Hassan 2016; Kwiatkowski 2021;

Maggio 2009; Maggio 2020; Olivieri 1997; Pennell 2006; Pennell 2014; Taher 2017; Vichinsky 2007).

Blinding of outcome assessment (detection bias)

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

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

We considered six trials to be at a high risk of detection bias as there was no description of blinding of outcome assessment, and it appears that investigators who were not blinded were also involved in outcome assessment (Bahnasawy 2017; Hassan 2016; Kwiatkowski 2021; Maggio 2020; Taher 2017; Vichinsky 2007).

Incomplete outcome data

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

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

We considered the rest of the trials to be at a high risk for attrition bias as there was no data on the flow and number of participants completing the trial; no participant numbers on AEs or compliance; no comparative data reported; per protocol analysis only; or large attrition bias in outcome analysis (Aydinok 2007; Badawy 2010; Bahnasawy 2017; Calvaruso 2014; El Beshlawy 2008; Kwiatkowski 2021; Maggio 2020; Olivieri 1997).

Selective reporting

We considered seven trials to be at a low risk of reporting bias as all identified outcomes were reported (Aydinok 2007; Calvaruso 2015; Kwiatkowski 2021; Maggio 2009; Maggio 2020; Olivieri 1997; Tanner 2007).

We considered five trials to be at an unclear risk of reporting bias because of either: minimal reporting of participant satisfaction and compliance; or no report of compliance with DFP; or unclear and selective reporting of AEs (Calvaruso 2014; Elalfy 2015; Galanello 2006a; Pennell 2014; Vichinsky 2007).

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

Other potential sources of bias

We considered five trials to be at a low risk as no other potential sources of bias were identified (Galanello 2006a; Maggio 2020; Mourad 2003; Pennell 2014; Tanner 2007).

We considered 13 trials to be at an unclear risk of other bias for various reasons including: baseline imbalances; abstract reports with insufficient details; no comparative numbers in control group; incomplete reporting of AEs; dose amendments after the start of the trial (Aydinok 2007; Badawy 2010; Bahnasawy 2017; Calvaruso 2014; Calvaruso 2015; Elalfy 2015; El Beshlawy 2008; Hassan 2016; Kwiatkowski 2021; Maggio 2009; Olivieri 1997; Taher 2017; Vichinsky 2007).

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

Effects of interventions

See: **Summary of findings 1** Summary of findings: Comparison 1 - deferiprone (DFP) versus deferoxamine (DFO); **Summary of findings 2** Summary of findings: Comparison 2 - deferasirox (DFX) versus deferiprone (DFO); **Summary of findings 3** Summary of findings: Comparison 3 - deferiprone (DFP) versus deferasirox (DFX); **Summary of findings 4** Summary of findings: Comparison 4 - deferasirox (DFX) film-coated tablets versus DFX dispersible tablets; **Summary of findings 5** Summary of findings: Comparison 5 - deferiprone (DFP) plus deferoxamine (DFO) versus DFP; **Summary of findings 6** Summary of findings: Comparison 6 - deferiprone (DFP) plus deferoxamine (DFO) versus DFO; **Summary of findings 7** Summary of findings: Comparison 7 - deferiprone (DFP) plus deferoxamine (DFO) versus DFP plus deferasirox (DFX); **Summary of findings 8** Summary of findings: Comparison 8 - medication management versus standard care

Results are presented for each of the main comparisons.

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

One abstract of a trial that included three review comparisons (deferiprone (DFP) versus deferoxamine (DFO); combination DFP and DFO versus DFP; combination DFP and DFO versus DFO) did not report any outcomes by intervention group and did not include counts of events (i.e. adverse events (AEs)), therefore we did not include this trial in the quantitative analysis (Badawy 2010). Thus, we have included 19 trials within the quantitative analysis.

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

The certainty of the evidence has been graded for those outcomes included in the summary of findings tables. For the definitions of these gradings, please refer to the summary of findings tables for

each comparison (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7; Summary of findings 8).

Comparison 1: DFP alone versus DFO alone

Seven randomised controlled trials (RCTs) were included in this comparison: four RCTs of thalassaemia major (Badawy 2010; El Beshlawy 2008; Olivieri 1997; Pennell 2006), one of thalassaemia intermedia (Calvaruso 2015), and two of sickle cell disease (SCD) (Calvaruso 2014; Kwiatkowski 2021). See Summary of findings 1. We downgraded the certainty of the evidence by either two for risk of bias due to high or unclear risk of bias in all domains or by one for imprecision due to wide CIs, or both.

Primary outcomes

1. Adherence to iron chelation therapy rates

All seven RCTs reported this outcome.

We are uncertain whether there is any difference in adherence to iron chelation therapy for oral DFP compared to subcutaneous DFO (two RCTs, 98 participants; very low-certainty evidence). Both trials implemented similar medication regimens (dose and frequency), although one trial included younger participants aged under 10 years (Olivieri 1997) compared to aged over 18 years in the second trial (Pennell 2006), which may have accounted for the significant heterogeneity (99%). Results could not be combined due to both a lack of data to report, as well as considerable heterogeneity between comparisons (I^2 = 99%) (Analysis 1.1). We identified the age of participants and differences in the medication regimens as possible explanations for heterogeneity.

We provide a narrative review of the data on compliance below and in Table 1.

The two RCTs reported mean (standard deviation, SD) rates of compliance; in the paediatric trial these were 94.9% (1.1%) in the DFP group (19 participants) and 71.6% (3.9%) in the DFO group (18 participants) (Olivieri 1997) and in the study of adults these were 94% (5.3%) in the DFP group (29 participants) and 93% (9.7%) in the DFO group (32 participants) (Pennell 2006).

Three trials reported mean compliance for each intervention group, but without reporting any error (SD or confidence interval (CI), etc.). The earlier Calvaruso trial (60 participants) reported mean compliance of 89% in the DFP group and 75% in the DFO group (Calvaruso 2014); the later Calvaruso trial similarly reported a higher mean rate of compliance in the DFP group (47 participants) 85% compared to the DFO group (41 participants) 76% (Calvaruso 2015); and Kwiatkowski reported compliance of 68.9% in the DFP group (152 participants) compared 78.9% in the DFO group (76 participants) with the additional comment, "treatment compliance similar throughout study" (P = 0.12) (Kwiatkowski 2021).

Two trials reported only narrative statements. In one trial (100 participants) the combined therapy group and DFP only group were more compliant to chelation therapy than the DFO only group, but the difference was statistically non-significant (Badawy 2010). The final trial (38 participants) reported that "four patients, all treated with DFO-based regimen, were excluded from the study due to lack of compliance. Compliance was otherwise excellent during the entire study period" (El Beshlawy 2008).

2. Serious adverse events (SAEs)

Three RCTs reported this outcome (Calvaruso 2014; Calvaruso 2015; Kwiatkowski 2021).

SAEs were analysed separately: total SAEs (from therapy, disease and non-adherence) (Analysis 1.2), where a total number of participants reporting SAEs had been reported; and other SAEs (from therapy, disease and non-adherence) (Analysis 1.3), where sub-categories of SAEs had been reported, could not be combined into a single pooled total due to the possibility of double-counting and have been presented using 99% CIs to avoid giving undue weight to any single category.

The Kwiatkowski trial (228 participants with SCD) reported a total number of SAEs at 12-month follow-up (risk ratio (RR) 1.43, 95% CI 0.83 to 2.46) (Analysis 1.2) (Kwiatkowski 2021).

Two RCTs reported SAEs in categories, but found no difference between groups for any of the reported categories (Analysis 1.3) (Calvaruso 2015; Kwiatkowski 2021). Calvaruso 2015 (88 participants with thalassaemia intermedia) reported only on agranulocytosis at 10-year follow-up (RR 7.88, 99% CI 0.18 to 352.39) (Calvaruso 2015). Kwiatkowski 2021 (228 participants with SCD) reported at 12-month follow-up on: pain crisis (RR 1.30, 99% CI 0.54 to 3.16); acute chest syndrome (RR 3.52, 99% CI 0.07 to 170.19); hepatic sequestration (RR 1.51, 99% CI 0.02 to 99.77); and chelation therapy-related events (RR 1.50, 99% CI 0.28 to 8.04) (Analysis 1.3).

3. All-cause mortality

Four RCTs reported this outcome: two in 288 participants with SCD (Calvaruso 2014; Kwiatkowski 2021); one in 61 participants with thalassaemia major (Pennell 2006); and one in 88 participants with thalassaemia intermedia (Calvaruso 2015).

Oral DFP may have little or no effect on all-cause mortality compared to subcutaneous DFO (RR 0.47, 95% CI 0.18 to 1.21; 3 RCTs, 376 participants; low-certainty evidence; Analysis 1.4).

No deaths occurred in the fourth trial (Pennell 2006).

Secondary outcomes

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

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

2. Health-related quality of life (QoL)

One RCT reported QoL (Kwiatkowski 2021); these data could not be analysed due to major bias as over half the sample was missing for this outcome, but we present the results in the tables (Table 13).

3. Iron overload

One RCT reported the proportion of participants with iron overload (Calvaruso 2015). We are uncertain if DFP reduces iron overload compared to DFO as defined as iron levels greater or equal to 800 (µg/L) (RR 1.31, 95% CI 0.49 to 3.48; 1 RCT, 38 participants; very low-certainty evidence; Analysis 1.5).

4. Organ damage

Two RCTs reported the proportion of participants with liver damage (Calvaruso 2014; Calvaruso 2015). We are uncertain if DFP increases the risk of liver damage compared to DFO (RR 5.13, 99% CI 0.54 to 48.40; 2 RCTs, 148 participants; very low-certainty evidence; Analysis 1.6).

5. Other AEs related to iron chelation

Four trials reported this outcome (Calvaruso 2015; El Beshlawy 2008; Kwiatkowski 2021; Pennell 2006). In people with thalassaemia taking DFP, we are uncertain if there is a difference in the risk of AEs compared to people taking DFO (Analysis 1.7).

Three RCTs reported on the risk of leukopenia (RR 3.95, 99% CI 0.37 to 41.87; 3 RCTs, 192 participants; very low-certainty evidence) and the risk of pain or swelling in joints (RR 3.55, 99% CI 0.49 to 25.81; 3 RCTs, 192 participants; very low-certainty evidence) (Calvaruso 2015; El Beshlawy 2008; Pennell 2006). Two RCTs reported on the risk of nausea or vomiting (RR 13.68, 99% CI 0.99 to 188.88; 2 RCTs, 132 participants; very low-certainty evidence) (Calvaruso 2015; El Beshlawy 2008). One RCT each reported on the risk of increased liver transaminase (RR 1.10, 99% CI 0.03 to 38.47; 1 RCT, 44 participants; very low-certainty evidence) (El Beshlawy 2008), local reactions at infusion sites (RR 0.17, 99% CI 0.00 to 9.12; 1 RCT, 88 participants; very low-certainty evidence) (Calvaruso 2015) and any other AEs related to iron chelation (RR 1.28, 95% CI 0.81 to 2.02; 1 RCT, 228 participants; very low-certainty evidence) (Kwiatkowski 2021).

Comparison 2: deferasirox (DFX) alone versus DFO alone

Three trials met the inclusion criteria for this comparison: two in thalassaemia (Hassan 2016; Pennell 2014), and one in SCD (Vichinsky 2007). See Summary of findings 2. We downgraded the certainty of evidence either by two due to high or uncertain risk of bias in several domains, or by one due to imprecision as the CIs are wide and there is only one trial with data in the comparison, or both.

Primary outcomes

1. Adherence to iron chelation therapy rates

All three trials reported on this outcome. Only one trial reported data in a format that could be incorporated into the analysis (Pennell 2014). We are uncertain if DFX increases the rate of adherence compared to people taking DFO (mean difference (MD) -1.40, 95% CI -3.66 to 0.86; 1 RCT, 197 participants with thalassaemia; very low-certainty evidence; Analysis 2.1).

The second trial in people with thalassaemia narratively reported that "throughout the study, all patients were compliant with the prescribed doses, and no discontinuation of drugs or drop-out of follow-up occurred" (Hassan 2016). The RCT in people with SCD reported that "the ratios of the administered to intended doses of therapy were high (1.16 for deferasirox and 0.97 for deferoxamine), indicating high adherence to the prescribed treatment regimens" (Vichinsky 2007).

2. SAEs

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

We are uncertain whether DFX affects the risk of disease-related SAEs in people with thalassaemia compared to DFO (RR 0.95, 95% CI 0.41 to 2.17; 2 RCTs, 247 participants; very low-certainty evidence; Analysis 2.2).

We are uncertain whether DFX affects the risk of SCD-related pain crisis (RR 1.05, 99% CI 0.59 to 1.86; 1 RCT, 195 participants; very low-certainty evidence; Analysis 2.3), or other SCD-related SAEs (RR 1.08, 99% CI 0.69 to 1.68; 1 RCT, 195 participants; very low-certainty evidence; Analysis 2.3).

3. All-cause mortality

Two trials report mortality (Hassan 2016; Pennell 2014). We are uncertain whether DFX has any effect on the risk of mortality in people with thalassaemia compared to DFO (RR 0.96, 95% CI 0.06 to 15.42; 2 RCTs, 240 participants; very low-certainty evidence; Analysis 2.4).

Secondary outcomes

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

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

2. Health-related QoL

No trials measured health-related QoL.

3. Iron overload

In people with thalassaemia we are uncertain whether DFX reduces the proportion of participants with serum ferritin of 1500 (µg/l) or higher (RR 1.18, 99% CI 0.52 to 2.68; 1 RCT, 60 participants; very low-certainty evidence; Analysis 2.5) (Hassan 2016). We are also uncertain whether DFX reduces the proportion of participants with severe liver iron concentration (LIC) defined as 15 mg Fe/g dry weight or higher (RR 1.00, 99% CI 0.78 to 1.27; very low-certainty evidence; Analysis 2.5)* (Pennell 2014), or myocardial T2* < 10 ms (RR 1.10, 99% CI 0.62 to 1.95; 1 RCT, 172 participants; very low-certainty evidence; Analysis 2.5)* (Pennell 2014).

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

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

4. Organ damage

No trial reported any other organ damage.

5. Other AEs related to iron chelation

Thalassaemia

We are uncertain whether there is any difference in the risk of total AEs related to iron chelation based on one RCT in people with thalassaemia (RR 1.15, 95% CI 0.76 to 1.73; 1 RCT, 187 participants; Analysis 2.6) (Pennell 2014).

Individual AEs related to iron chelation were analysed separately and presented with 99% CI (Analysis 2.7). We are uncertain whether there are any differences between the groups for the risk of:

gastrointestinal upset (RR 3.00, 99% CI 0.41 to 22.06; 1 RCT, 60 participants; very low-certainty evidence) (Hassan 2016); rash (RR 3.05, 99% CI 0.69 to 13.51; 2 RCTs, 247 participants; very low-certainty evidence) (Hassan 2016; Pennell 2014); increased blood creatinine (RR 3.79, 99% CI 0.51 to 28.05; 1 RCT, 187 participants; very low-certainty evidence) (Pennell 2014); proteinuria (RR 2.21, 99% CI 0.39 to 12.56; 1 RCT, 187 participants; very low-certainty evidence) (Pennell 2014); increased alanine aminotransferase (ALT) (RR 5.69, 99% CI 0.36 to 89.55; 1 RCT, 187 participants; very low-certainty evidence) (Pennell 2014); increased aspartate aminotransferase (AST) (RR 5.69 99% CI 0.36 to 89.55; 1 RCT, 187 participants; very low-certainty evidence) (Pennell 2014); diarrhoea (RR 5.69, 99% CI 0.36 to 89.55; 1 RCT, 187 participants; very low-certainty evidence) (Pennell 2014); or vomiting (RR 6.64, 99% CI 0.14 to 320.288; 1 RCT, 187 participants; very low-certainty evidence) (Pennell 2014).

In people with thalassaemia, we are uncertain whether DFX reduces the incidence of total AEs as compared to DFO (RR 0.89, 95% CI 0.75 to 1.07; 1 RCT, 187 participants; very low-certainty evidence; Analysis 2.8) (Pennell 2014).

We downgraded the certainty of evidence either by two due to high or uncertain risk of bias in several domains, or by one due to imprecision as the CIs are wide and there is only one trial with data in each comparison, or both.

SCD

One RCT contributed to this outcome (Vichinsky 2007). In people with SCD, DFX compared to DFO may increase slightly the risk of: abdominal pain (RR 1.91, 99% CI 0.80 to 4.58; 1 RCT, 195 participants; low-certainty evidence; Analysis 2.9); diarrhoea (RR 4.14, 99% CI 0.90 to 18.92; 1 RCT, 195 participants; low-certainty evidence; Analysis 2.9); and nausea or vomiting (RR 1.63, 99% CI 0.90 to 2.94; 1 RCT, 195 participants; low-certainty evidence; Analysis 2.9). We are uncertain if DFX compared to DFO affects the risk of an increase in ALT (RR 5.29, 99% CI 0.12 to 232.98; 1 RCT, 195 participants; low-certainty evidence; Analysis 2.9) or the risk of pain or swelling in joints (RR 1.06, 99% CI 0.41 to 2.76; 1 RCT, 195 participants; very low-certainty evidence; Analysis 2.9).

Comparison 3: DFP versus DFX

One RCT reported for this comparison (Maggio 2020). See Summary of findings 3. We downgraded the quality of evidence by either two for risk of bias due to high or unclear risk of bias in all domains, or by one for imprecision due to wide CIs, or both.

Primary outcomes

1. Adherence to iron chelation therapy

We are uncertain if there is a difference between groups for adherence at 12 months (MD -3.00%, 95% CI -6.56 to 0.56; 1 RCT, 309 participants; low-certainty evidence; Analysis 3.1).

2. SAEs

We are uncertain if there is a difference between groups for either total SAEs at 12 months (RR 0.95, 95% CI 0.46 to 1.96; 1 RCT, 390 participants; very low-certainty evidence; Analysis 3.2) or chelation-related SAEs at 12 months (Peto odds ratio (OR) 1.54, 95% CI 0.44 to 5.39; 1 RCT, 390 participants; very low-certainty evidence; Analysis 3.3).

3. All-cause mortality

We are uncertain if there is a difference between groups at 12 months as there were zero deaths in either group (risk difference (RD) 0.00, 95% CI -0.01 to 0.01; 1 RCT, 390 participants; low-certainty evidence; Analysis 3.4).

Secondary outcomes

1. Sustained adherence to therapy

As the end of trial was beyond six months, these results have been reported above under the primary outcome measure.

2. Health-related QOL

This outcome was not reported for this comparison.

3. Iron overload

This outcome was not reported for this comparison.

4. Organ damage

This outcome was not reported for this comparison.

5. Other AEs related to iron chelation

This outcome was not reported for this comparison.

Comparison 4: DFX film-coated tablet (FCT) versus DFX dispersible tablet (DT)

One RCT in individuals with thalassaemia met the inclusion criteria for this comparison (Taher 2017). See Summary of findings 4. We downgraded the certainty of the evidence by either two for risk of bias due to high or unclear risk of bias in all domains, by one for imprecision due to wide CIs, or both.

Primary outcomes

1. Adherence to iron chelation therapy rates

Taher 2017 reported adherence as the number of participants adhering to the trial protocol (n/N). We are uncertain if there is a preference for FCT (RR 1.10, 95% CI 0.99 to 1.22; 1 RCT, 173 participants; very low-certainty evidence; Analysis 4.1).

At 13 weeks, we are uncertain if there is a difference in percentage compliance (assessed via pill count) between groups (MD 5.00%, 95% CI -6.75 to 16.75; 1 RCT, 91 participants; very low-certainty evidence; Analysis 4.2).

2. SAEs

We are uncertain if DFX FCT has any effect on SAEs as compared to DFX DT (RR 1.22, 95% CI 0.62 to 2.37; 1 RCT, 173 participants; very low-certainty evidence; Analysis 4.3).

3. All-cause mortality

We are uncertain if DFX FCT increases all-cause mortality as compared to DFX DT (Peto OR 7.30, 95% CI 0.14 to 368.15; 1 RCT, 173 participants; very low-certainty evidence; Analysis 4.4).

Secondary outcomes

1. Sustained adherence to therapy

At 24 weeks, we are uncertain if there is a difference in percentage compliance (assessed via pill count) between groups (MD 7.00%,

95% CI -8.94 to 22.94; 1 RCT, 54 participants, very low-certainty evidence; Analysis 4.2).

2. Health-related QoL

This outcome was not measured with a validated instrument.

3. Iron overload

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

4. Organ damage

We are uncertain if there is a difference between groups for the incidence of renal events (RR 1.25, 99% CI 0.72 to 2.18; 1 RCT, 173 participants; very low-certainty evidence; Analysis 4.5).

5. Other AEs related to iron chelation

We are uncertain if there is a benefit from FCT for total chelation-related AEs (RR 0.75, 95% CI 0.57 to 0.99; 1 RCT, 173 participants; very low-certainty evidence; Analysis 4.6).

We are uncertain if there is a difference between groups for: the risk of diarrhoea (RR 0.70, 99% CI 0.29 to 1.70; 1 RCT, 173 participants; Analysis 4.7); increased urine protein/urine creatinine ratio (RR 1.65, 99% CI 0.60 to 4.54; 1 RCT, 173 participants; Analysis 4.7); the incidence of abdominal pain (RR 0.49, 99% CI 0.16 to 1.52; 1 RCT, 173 participants; Analysis 4.7); or the incidence of nausea (RR 0.72, 99% CI 0.23 to 2.23; 1 RCT, 173 participants; Analysis 4.7).

We are uncertain if there is a difference in favour of FCT for incidence of vomiting (RR 0.28, 99% CI 0.07 to 1.15; 1 RCT, 173 participants; very low-certainty evidence; Analysis 4.7).

Comparison 5: DFP and DFO combination therapy versus DFP alone

Four trials in people with thalassaemia met the inclusion criteria for this comparison (Aydinok 2007; Badawy 2010; El Beshlawy 2008; Maggio 2009). We were not able to extract data from one trial (Badawy 2010). See Summary of findings 5. We downgraded the certainty of evidence by either two for risk of bias due to high or unclear risk of bias in several domains in all trials, or by one due to imprecision, because the effect estimates have wide CIs, or both.

Primary outcomes

1. Adherence to iron chelation therapy rates

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

One trial (24 participants) reported that "Compliance was generally excellent during the entire study period. There was only one patient in the DFP treatment arm who missed more than one chelation dose per week because of problems with swallowing" (Aydinok 2007). A second trial (36 participants) reported that "four patients, all treated with DFO-based regimen, were excluded from the study due to lack of compliance. Compliance was otherwise excellent during the entire study period" (El Beshlawy 2008). The third trial (108 participants) reported that "In the sequential DFP–DFO group, compliance was 92.7% (SD ± 15.2%; range 37 to 100%) with DFP treatment and 70.6% (SD ± 24.1%; range 25 to 100%) with DFO treatment (105 participants). Compliance with DFP was 93.6% (SD ± 9.7%; range 56 to 100%) in the DFP-alone patients" (Maggio 2009).

2. SAEs

Only one trial reported this outcome (Maggio 2009). In people with thalassaemia, combination therapy with DFP and DFO may make little or no difference to the incidence of SAEs as compared to DFP alone (RR 0.15, 95% CI 0.01 to 2.81; 1 RCT, 213 participants; low-certainty evidence; Analysis 5.1).

3. All-cause mortality

Two trials reported on this outcome (Aydinok 2007; Maggio 2009). We are uncertain if combination therapy with DFP and DFO decreases mortality as compared to DFP alone (Peto OR 0.77, 95% CI 0.17 to 3.42; 2 RCTs, 237 participants; very low-certainty evidence; Analysis 5.2).

Secondary outcomes

1. Sustained adherence to therapy

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

2. Health-related QoL

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

3. Iron overload

No trial reported the proportion of participants with iron overload.

4. Organ damage

No trial reported the proportion of participants with organ damage.

5. Other AEs related to iron chelation

Three RCTs reported chelation therapy-related AEs (Aydinok 2007; El Beshlawy 2008; Maggio 2009). We could not calculate a total incidence, and so have presented the separate categories of AEs and reported using a 99% CI (Analysis 5.3).

We are uncertain if there is any difference in the risks of chelation therapy-related AEs: leukopenia, neutropenia or agranulocytosis (or a combination of) (RR 1.15, 99% CI 0.50 to 2.62; 3 RCTs, 280 participants; very low-certainty evidence) (Aydinok 2007; El Beshlawy 2008; Maggio 2009); pain or swelling in joints (RR 0.76, 99% CI 0.31 to 1.91; 2 RCTs, 256 participants; very low-certainty evidence) (El Beshlawy 2008; Maggio 2009); gastrointestinal disturbances (RR 0.45, 99% CI 0.15 to 1.37; 1 RCT, 213 participants; very low-certainty evidence) (Maggio 2009); increased liver transaminase (RR 1.02, 99% CI 0.52 to 1.98; 2 RCTs, 256 participants; very low-certainty evidence) (El Beshlawy 2008; Maggio 2009); or nausea or vomiting (RR 0.55, 99% CI 0.13 to 2.23; 1 RCT, 43 participants; very low-certainty evidence) (El Beshlawy 2008).

Comparison 6: DFP and DFO combination therapy versus DFO alone

Five trials in people with thalassaemia met the inclusion criteria for this comparison (Badawy 2010; El Beshlawy 2008; Galanello 2006a; Mourad 2003; Tanner 2007). See Summary of findings 6. We downgraded the certainty of the evidence by two for risk of bias due to high or unclear risk of bias in several domains in all trials and by one due to imprecision, as the effect estimates have wide CIs.

Primary outcomes

1. Adherence to iron chelation therapy rates

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

Four trials reported on this outcome (El Beshlawy 2008; Galanello 2006a; Mourad 2003; Tanner 2007). Three trials gave some basic data: one trial reported that in the DFP/DFO group (29 participants) the mean (SD) compliance was 96.1% (5.0) for DFO but DFP compliance was not reported; for the DFO alone group (30 participants) mean (SD) compliance was 95.7% (5.7) (Galanello 2006a). The second trial reported that "Compliance with deferoxamine was similar in both groups (combined 91.4 ± 2.7% versus deferoxamine 92.6 ± 2.7%; P = 0.7). Compliance with deferiprone was less than compliance with placebo (82.4 ± 18.1% versus 89.8 ± 7.2%; P = 0.04)" (Tanner 2007). The final trial reported that "In patients receiving the combined therapy, compliance was excellent (arbitrarily defined as taking > 90% of the recommended doses) in 10 patients and good (75% to 90% of recommended doses) in one patient, as assessed by the patient's history, parental evidence and usage of tablets provided in just sufficient quantities between check-up visits. In patients receiving DFX alone, compliance was considered to be excellent in 11 patients and good in three patients, as assessed mainly by counting the vials given to, and returned by, the patients" (Mourad 2003).

The remaining trial provided a narrative report that "four patients, all treated with DFO-based regimen, were excluded from the study due to lack of compliance. Compliance was otherwise excellent during the entire study period" (El Beshlawy 2008).

2. SAEs

Three RCTs (142 participants) assessed SAEs and reported that no SAEs occurred (Galanello 2006a; Mourad 2003; Tanner 2007).

3. All-cause mortality

Only one trial (65 participants) assessed this outcome and reported that no deaths occurred (Tanner 2007).

Secondary outcomes

1. Sustained adherence to therapy

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

2. Health-related QoL

No trials measured QoL.

3. Iron overload

No trials reported the proportion of participants with iron overload.

4. Organ damage

No trials reported the proportion of participants with organ damage.

5. Other AEs related to iron chelation

All four trials reported the incidence of AEs by category or type (therefore these are presented with 99% CI (Analysis 6.1)).

We are uncertain if DFP combined with DFO reduces other chelation-related AEs compared to DFO alone in people with thalassaemia (Analysis 6.1): risk of leukopenia, neutropenia or agranulocytosis (or a combination of) (RR 1.18, 99% CI 0.09 to 15.45; 3 RCTs, 169 participants; very low-certainty evidence) (El Beshlawy 2008; Galanello 2006a; Tanner 2007); risk of pain or swelling in joints (RR 2.41, 99% CI 0.17 to 34.41; I^2 = 66%; 3 RCTs, 135 participants; very low-certainty evidence) (El Beshlawy 2008; Mourad 2003; Tanner 2007); risk of increased liver transaminase (RR 3.46, 99% CI 0.45 to 26.62; 2 RCTs, 104 participants; very low-certainty evidence) (El Beshlawy 2008; Galanello 2006a); risk of nausea or vomiting (RR 4.34, 99% CI 0.77 to 24.44; 4 RCTs, 194 participants; very low-certainty evidence) (El Beshlawy 2008; Galanello 2006a; Mourad 2003; Tanner 2007); and risk of local reactions at infusion site (RR 0.18, 99% CI 0.01 to 4.43; 2 RCTs, 90 participants; very low-certainty evidence) (Mourad 2003; Tanner 2007).

Comparison 7: DFP and DFO combination therapy versus DFP and DFX combination therapy

One RCT in people with thalassaemia met the inclusion criteria for this comparison (Elalfy 2015). See Summary of findings 7. We downgraded the certainty of evidence by one for risk of bias as there was a high or unclear risk of bias in three domains; by one for indirectness, as the trial was conducted in children aged 10 to 18 years with severe iron overload; and by one due to imprecision, as the effect estimates have wide CIs.

Primary outcomes

1. Adherence to iron chelation therapy rates

In children with thalassaemia, combination therapy with DFP and DFX may improve adherence to iron chelation therapy compared to combination therapy with DFP and DFO (RR 0.84, 95% CI 0.72 to 0.99; 1 RCT, 96 participants; low-certainty evidence; Analysis 7.1).

2. SAEs

In children with thalassaemia, we are uncertain if combination therapy with DFP and DFX decreases the incidence of SAEs compared to combination therapy with DFP and DFO (Peto OR 1.00, 95% CI 0.06 to 16.22; 1 RCT, 96 participants; very low-certainty evidence; Analysis 7.2).

3. All-cause mortality

In children with thalassaemia, combination therapy with DFP and DFX may make little or no difference to mortality compared to combination therapy with DFP and DFO. There were no deaths in the trial (RR 0.00, 95% -0.04 to 0.04; 1 RCT, 96 participants; low-certainty evidence; Analysis 7.3).

Secondary outcomes

1. Sustained adherence to therapy

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

2. Health-related QoL

In children with thalassaemia we are unclear if combination therapy with DFP and DFX improves QoL compared to combination therapy with DFP and DFO (very low-certainty evidence). The authors state that "significant improvement in QoL was observed in both groups at study end compared to baseline (P < 0.001)"; no usable comparative data were provided, as it was presented on a bar chart only, stating that group difference at the study endpoint was not different (P = 0.297).

3. Iron overload

Proportion of participants with iron overload was not reported.

4. Organ damage

In children with thalassaemia, there may be little or no difference between groups in the incidence of increased creatinine (at least 33% above baseline levels) between groups (RR 3.00, 99% CI 0.16 to 56.04; 1 RCT, 96 participants; low-certainty evidence; Analysis 7.4).

5. Other AEs related to iron chelation

In children with thalassaemia, we are uncertain if there is a difference between groups for the total incidence of AEs related to iron chelation at one year (RR 1.08, 95% CI 0.76 to 1.53; 1 RCT, 96 participants; very low-certainty evidence; Analysis 7.5).

The RCT also reported AEs by category. We are uncertain if there is a difference between the two groups for: the risk of leukopenia, neutropenia or agranulocytosis (RR 1.67, 99% CI 0.27 to 10.14; 1 RCT, 96 participants; Analysis 7.6); the risk of pain or swelling in joints (RR 0.89, 99% CI 0.29 to 2.77; 1 RCT, 96 participants; Analysis 7.6); gastrointestinal problems (RR 0.60, 99% CI 0.18 to 2.04; 1 RCT, 96 participants; Analysis 7.6); increased liver transaminase (RR 1.33, 99% CI 0.20 to 8.88; 1 RCT, 96 participants; Analysis 7.6); or skin rash (RR 5.00, 99% CI 0.10 to 261.34; 1 RCT, 96 participants; Analysis 7.6).

Comparison 8: Medication management versus standard care

One six-month RCT in people with thalassaemia met the inclusion criteria for this comparison (Bahnasawy 2017). See Summary of findings 8. We downgraded the quality of evidence by either two for risk of bias due to high or unclear risk of bias in all domains or by one for indirectness because most outcomes were only reported in the intervention group.

Primary outcomes

1. Adherence to iron chelation therapy rates

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

2. SAEs

SAEs were not reported.

3. All-cause mortality

All-cause mortality was not reported.

Secondary outcomes

1. Sustained adherence to therapy

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

2. Health-related QoL

We are uncertain if medication management improves health-related QoL as measured by the Pediatric Quality of Life Inventory TM (PedsQLTM) in the single trial (48 participants) in this comparison. The total median (interquartile range (IQR)) score in the test group was 63.51 (51.75 to 84.54) compared to 49.84 (41.9 to 60.81) in the control group (very low-certainty evidence).

3. Iron overload

The proportion of participants with iron overload was not reported.

4. Organ damage

The proportion of participants with organ damage was not reported.

5. Other AEs related to iron chelation

AEs were not reported.

Comparison 9: Education versus standard care

One quasi-experimental trial (NRSI) reported for this comparison (Gharaati 2019), but due to severe baseline confounding, we do not feel it is appropriate to report the findings of this trial.

DISCUSSION

People with SCD and people with transfusion-dependent or non-transfusion-dependent thalassaemia, who undergo regular blood transfusions, are at risk of iron overload. Iron overload can lead to iron toxicity, with organs such as the heart, liver and endocrine glands being particularly vulnerable.

In this review we examined the evidence for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia. A total of 20 trials (19 RCTs and one NRSI) met our inclusion criteria. Fourteen trials included people with β-thalassaemia major, one included people with thalassaemia intermedia, two included people with SCD only, and the remainder assessed a mixture of people with iron overload with SCD, thalassaemia and other haemoglobinopathies. Included trials were published between 1997 and 2021; 18 included trials were medication interventions, one assessed a medication management intervention and one (NRSI) assessed an education intervention.

We also identified four ongoing RCTs, and 13 studies are awaiting classification (often due to unclear study design). We did not identify any cluster-RCTs, CBA or ITS studies that met the inclusion criteria.

Summary of main results

We grouped the data into nine comparisons of interest.

1. DFP (oral) versus DFO (subcutaneous)

Based on results from four trials in thalassaemia, we are uncertain whether oral DFP increases adherence to iron chelation therapy more than subcutaneous DFO (Calvaruso 2015; El Beshlawy 2008; Olivieri 1997; Pennell 2006). We were not able to combine results due to a lack of data to report as well as the considerable heterogeneity between comparisons (I^2 = 99%). There was high adherence in all trials; however, there was significant loss to follow-

up and the number of participants assessed for adherence was generally small (n < 50).

The reporting of SAEs was variable and we are uncertain if there is any difference between the different intervention groups as CIs were very wide, so there was very low certainty about the result. We are uncertain if there is a difference in all-cause mortality between the two groups. QoL could not be analysed due to major bias in the sample (large loss to follow-up).

2. DFX (oral) versus DFO (subcutaneous)

Based on results from three trials (unpooled), two in thalassaemia (Hassan 2016; Pennell 2014) and one in SCD (Vichinsky 2007), we are uncertain if there is a difference in adherence between the two drug interventions; participants had high adherence in all trials (SCD and thalassaemia).

We are uncertain if there is a difference between the drug therapies in SAEs (SCD or thalassaemia) or all-cause mortality (thalassaemia). No trial in this comparison reported on QoL.

3. DFP (oral) versus DFX (oral, dispersible)

Very low-certainty evidence from a single trial in children (average age 9 to 10 years) of any hereditary haemoglobinopathy requiring chronic transfusion therapy and chelation means we are uncertain if there is a difference between oral DFP and DFX in adherence, SAEs and all-cause mortality, to the trial endpoint at 12 months.

4. DFX (FCT) versus DFX (DT)

Based on results from a single trial in people with thalassaemia (Taher 2017), there may be a preference shown through greater adherence to FCT over dispersible formulations, though this was not replicated in measures of compliance (no difference in the pill count at 13 weeks). There was high adherence in both arms of the trial.

We are uncertain if there is a difference in incidence of SAEs, all-cause mortality or sustained adherence at 24 weeks. We are uncertain if there is a benefit with FCT in chelation-related AEs. The trial did not measure QoL using a validated instrument.

5. DFP and DFO combined versus DFP alone

Based on results from three trials in people with thalassaemia, we cannot determine if there is a difference in adherence, as investigators generally reported that adherence was "excellent" for both groups (Aydinok 2007; El Beshlawy 2008; Maggio 2009). There may be little or no difference in the incidence of SAEs and mortality. We could not assess QoL, although it was reported, as it was not measured using a validated instrument.

6. DFP and DFO combined versus DFO alone

Based on results from four trials in people with thalassaemia, there may be little or no difference to adherence rates, SAEs (none reported in the trial period) or mortality (none reported in trial period) (El Beshlawy 2008; Galanello 2006a; Mourad 2003; Tanner 2007). There was high adherence in all trials. QoL was not measured in any trial in this comparison.

7. DFP and DFO combined versus DFP and DFX combined

Based on the results of a single trial in children with thalassaemia, combination therapy with DFP and DFX may improve adherence to iron chelation therapy compared to combination therapy with DFP and DFO (Elalfy 2015). There was high adherence (over 80%) in both arms. We are uncertain if there is a difference in the incidence of SAEs, and no deaths were reported during the trial, so we can draw no conclusions about the impact on mortality. Investigators reported QoL narratively, suggesting a benefit in both groups.

8. Medication management versus standard care

Very low-certainty evidence from a single trial in people with thalassaemia reported on this comparison (Bahnasawy 2017). Adherence rates were only reported in the intervention arm and therefore there are no comparative data to analyse. We are uncertain if medication management improves health-related QoL.

9. Education versus standard care

On quasi-experimental (NRSI) study could not be analysed due to the severe baseline confounding (Gharaati 2019), so the evidence could not be assessed.

Overall completeness and applicability of evidence

This review provides the most up-to-date assessment of interventions to improve adherence to iron chelation therapy in people with sickle cell disease and thalassaemia. We have also identified four ongoing trials and 13 trials that are awaiting classification due to insufficient information to reach a decision to either include or exclude.

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

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

Quality of the evidence

Overall we rated the certainty of the evidence according to GRADE methodology across all comparisons for the outcomes of adherence, SAEs and mortality as low to very low (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7; Summary of findings 8)

We downgraded the certainty of the evidence for high and unclear risk of bias (randomisation process, lack of blinding, large dropout or incomplete outcome reporting), imprecision (wide CIs around the effect estimate and small sample sizes far below the optimal information size required for the outcomes of interest) and indirectness (lack of direct evidence pertinent to our population of interest). Our outcome of QoL was largely not reported, reported using non-validated measurements or insufficiently reported (e.g. missing data, not reported by group).

Potential biases in the review process

To our knowledge, our review process was free from bias. We conducted a comprehensive search, searching data sources (including multiple databases, and clinical trial registries) to ensure that all relevant trials would be captured. There were no restrictions for the language in which the paper was originally published. We carefully assessed the relevance of each paper and performed all screening and data extractions in duplicate. We pre-specified all outcomes and subgroups prior to analysis. We were unable to assess publication bias using funnel plots as no individual outcome in a single comparison included enough trials (fewer than 10 trials).

Agreements and disagreements with other studies or reviews

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

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

AUTHORS' CONCLUSIONS

Implications for practice

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

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

Implications for research

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

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Aydinok 2007

Study characteristics	
Methods	**Study design**: single-centre RCT **Study grouping**: parallel-group **Study duration**: treatment duration 12 months; follow-up: not stated
Participants	**Baseline characteristics** **DFP, DFO** • Total # of participants: 12 randomised; 8 analysed • Age mean (SD): 16.6 (4.8) years, range 9 to 23 years • Sex: not reported • Ethnicity: not reported • Thalassaemia genotype N (%): 100% β-thalassaemia • Baseline ferritin levels (ng/mL) mean (SD): 4453 (2858) • Previous iron chelation: not reported • Duration of any iron chelation: not reported • LIC (mg/g) mean (SD): 27.0 (13.4) • Splenectomy n (%): not reported • QoL (mean (SD)): not reported • Hb, g/L mean (SD): 89 (5) **DFP** • Total # of participants: 12 • Age mean (SD): 15.9 (4.2) years • Sex: not reported • Ethnicity: not reported • Thalassaemia genotype N (%): 100% β-thalassaemia • Baseline ferritin levels (ng/mL): 4070 (3223) • Previous iron chelation: not reported • Duration of any iron chelation: not reported • LIC (mg/g): 30.7 (10.6) • Splenectomy n (%): not reported • QoL (mean (SD)): not reported • Hb, g/L mean (SD): 89 (5), range 9 to 23 years

Aydinok 2007 *(Continued)*

	Inclusion criteria: iron-overloaded people with thalassaemia at least 4 years old **Exclusion criteria**: lack of compliance, known toxicity or intolerance preventing therapy with DFO and DFP, neutropenia (neutrophils < 1.5×10^9/L), thrombocytopenia (platelets < 100×10^9/L), renal, hepatic or decompensated heart failure, active viral illness being treated with interferon-α/ribavirin, repeated Yersinia infections, HIV–positivity, pregnancy or nursing, and patients of reproductive age not taking adequate contraceptive precautions
Interventions	**Treatment arm**: DFO (50 mg/kg/day subcutaneously twice-weekly (mean (SD) dose: 43.8 (2.8) mg/kg)) combined with DFP (75 mg/kg/day, daily (mean (SD) dose: 78.2 (1.4) mg/kg/day)) **Comparator arm**: DFP (75 mg/kg/day, daily (mean (SD) dose: 78.2 (2.6) mg/kg/day))
Outcomes	**Adherence**: compliance was assessed by drug accounting at each visit (by counting the returned empty blisters of DFP and used vials of DFO) as well as by a trial-specific questionnaire completed by the participants and/or their legal representative/guardian at quarterly intervals. The same questionnaire also served for the assessment of tolerance to treatment and QoL **Trial-reported outcomes** 1. Changes in LIC and SF (primary outcome) 2. Total iron excretion 3. Urinary iron excretion 4. Iron balance 5. Cardiac function (Echo) 6. Toxicity 7. Assessment of tolerance to treatment and QoL
Identification	Source of funding: none stated, although the drugs were supplied by Lipomed AG, Switzerland
Notes	All participants had prior exposure to DFO (dose, schedule and duration were not reported) and all had a washout period of 2 weeks with no iron chelation before initiating trial treatment Sample size calculation not reported **Country**: Turkey

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization sequence was generated by the Department of Mathematical Statistics at the University of Berne, Switzerland according to local policy". Following central registration of a subject by the investigator, the trial co-ordinator assigned the intervention according to the randomisation sequence.
Allocation concealment (selection bias)	High risk	The trial report states that the intervention was assigned according to the randomisation sequence “without concealing the sequence prior to allocation”
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	The authors did not report any information as to whether participants, personnel were blinded to treatment allocation but one treatment was subcutaneous and other oral so difficult to blind
Blinding of outcome assessment (detection bias) All outcomes except mortality	Unclear risk	The authors did not report any information as to whether outcome assessors were blinded to treatment allocation

Aydinok 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	There was an imbalance in missing data across the treatment arms. 4 participants from the comparator group (DFO) were not included in the outcome analysis: 2 withdrew consent due to refusal to take DFO; 1 died from arrhythmia induced congestive heart failure at start of trial; and 1 developed agranulocytosis at week 14
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Unclear risk	There is an imbalance in baseline LIC and ferritin between groups

Badawy 2010

Study characteristics	
Methods	**Study design**: RCT **Study grouping**: parallel-group Length of trial or follow-up not stated. Not stated if open-label; but no mention of blinding and DFO is infusion versus tablet
Participants	**Baseline characteristics** **DFP, DFO** • Total # of participants: 50 • Age: ≥ 8 years • Sex: not reported • Ethnicity: not reported • Thalassaemia genotype N (%): 100% β-thalassaemia • Baseline ferritin levels (ng/mL): not reported • Previous iron chelation: DFO • Duration of any iron chelation: not reported • LIC (mg/g): not reported • Splenectomy n (%): not reported • QoL (mean (SD)): not reported • Hb, g/L: not reported **DFP** • Total # of participants: 50 • Age: ≥ 8 years • Sex: not reported • Ethnicity: not reported • Thalassaemia genotype N (%): β-thalassaemia • Baseline ferritin levels (ng/mL): not reported • Previous iron chelation: DFO • Duration of any iron chelation: not reported • Liver iron concentration LIC (mg/g): not reported • Splenectomy n (%): not reported • QoL (mean (SD)): not reported • Hb, g/L: not reported **DFO**

Badawy 2010 *(Continued)*

- Total # of participants: 50
- Age: greater or equal to 8 years
- Thalassaemia genotype N (%): 100% β-thalassaemia
- Baseline ferritin levels (ng/mL): not reported
- Previous iron chelation: DFO
- Duration of any iron chelation: not reported
- LIC (mg/g): not reported
- Splenectomy n (%): not reported
- QoL (mean (SD)): not reported
- Hb, g/L: not reported

Inclusion criteria: 8 years, RBC transfusion every 3 to 4 weeks, on DFO prior to study as single therapy

Exclusion criteria: not stated

Participants PRBCs /3 to 4 weeks to maintain Hb > 9 g/dL

Interventions	**DFP, DFO** • Medication intervention: daily DFP, DFO twice-weekly DFO (40 mg/kg/day); DFP (75 mg/kg/day) **DFP** • Medication intervention: daily DFP (75 mg/kg/day) **DFO** • Medication intervention: DFO 5 days/week DFO (40 mg/kg/day)
Outcomes	**Adherence** to iron chelation therapy rates Questionnaire on chelation therapy, reasons for non-compliance, side effects, life activities, transfusion regimen **Trial-reported outcomes** • CBC monthly • SF levels • Liver and kidney functions • Blood glucose level • Serum calcium and phosphorus/3 months and T3, T4, TSH, LH, FSH • Echocardiography • Bone density • Auditory and visual examination twice
Identification	**Sponsorship source**: Zagazig University Hospital, Zagazig **Country**: Egypt **Setting**: University Hospital **Comments**: Abstract Poster 124 **Author's name**: Sherif Badawy **Institution**: Ann Robert H. Lurie Children's Hospital of Chicago **Email**: sbadawy@luriechildrens.org **Address**: Ann Robert H. Lurie Children's Hospital of Chicago Northwestern University Feinberg School of Medicine225 East Chicago Avenue, Box 30, Chicago, Illinois 60611-2605

Badawy 2010 *(Continued)*

Notes	Contacted author and study data not available at this time. Sample size calculation not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: no description of sequence generation
Allocation concealment (selection bias)	Unclear risk	Judgement comment: no description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Judgement comment: no description, but one drug is subcutaneous injection (DFO). Open-label
Blinding of outcome assessment (detection bias) All outcomes except mortality	Unclear risk	Judgement comment: no description of blinding of assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: no data on number of participants who completed the study and how many in each group experienced complications. Lack of detail on number of compliant or non-compliant participants.
Selective reporting (reporting bias)	High risk	Judgement comment: not clear which groups and how many experienced adverse events. No data reported on SF or other outcomes.
Other bias	Unclear risk	Judgement comment: results of the trial were not published in detail and no data available when authors were contacted

Bahnasawy 2017

Study characteristics

Methods	**Study design**: single-centre RCT **Study grouping**: parallel-group **Study duration**: 6 months
Participants	**Baseline characteristics** Comprehensive medication management • Total # of participants: 24 • Age (mean (SD)): 12 (2.7) years • Sex N (%): 15 (62.5) female; 9 (37.5) male • Ethnicity: NR • Thalassaemia genotype (%): β-thalassaemia major 100% • Baseline ferritin levels (ng/mL) (mean (SD)): 3949 (1864) • Previous iron chelation: N/A • Duration of any iron chelation: N/A

Bahnasawy 2017 *(Continued)*

- LIC (mg/g): not stated
- Splenectomy n (%): 6 (25.9)
- QoL PedsQL median (IQR): 55.16 (43.42 to 63.75)
- Hb, g/L: not stated

Standard care (as defined in the trial)

- Total # of participants: 24
- Age (mean (SD)): 13 (2.8)
- Sex N (%): F: 15 (62.5); M: 9 (37.5)
- Ethnicity: not reported
- Thalassaemia genotype (%): β-thalassaemia major 100%
- Baseline ferritin levels (ng/mL) (mean (SD)): 3871 (1881)
- Previous iron chelation: N/A
- Duration of any iron chelation: N/A
- LIC (mg/g): not stated
- Splenectomy n (%): 9 (37.5)
- QoL PedsQL median (IQR): 49.12 (38.13 to 56.95)
- Hb, g/L: not stated

Inclusion criteria: transfusion-dependent children with β-thalassaemia major aged 8 to 18 years with SF level of more than 1000 µg/L

Exclusion criteria: people with cognitive impairment

Interventions	**Comprehensive medication management** • Interview with participants at each visit, drug-related problems identified, care plan introduced/monitored to include dosage modification, education. Follow-up compliance via regular phone calls. **Standard care (as defined in the trial)** • All participants presented to the clinic regularly every 2 to 4 weeks according to the need for receiving blood transfusion, blood samples were drawn for CBC assessment. Physical examination was done by physician including assessment of hepatomegaly, splenomegaly and any health-related problems.
Outcomes	**Adherence** to iron chelation therapy rates "DRP identification: The clinical pharmacist analysed the collected data to detect whether any DRPs existed and allocated them to one of the seven categories as classified by Cipolle et al. [18]: unnecessary drug therapy, need for additional drug therapy, ineffective drug product, dosage too low, adverse drug reaction, dosage too high, non-compliance" **Trial-reported outcomes** 1. SF levels were measured at baseline, 3 months and after 6 months 2. CBC with WBC differential was assessed at every visit, and SCr and ALT were measured routinely for all the participants every 3 months 3. Health-related QoL was assessed at baseline and at the end of the trial (after 6 months) using PedsQL™ 4.0 Generic Core Scale questionnaire. PedsQL is a 23-item multidimensional model with 4 domains for paediatric health-related QoL measurement: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items) and school functioning (5 items) (19).
Identification	**Sponsorship source**: not stated **Country**: Egypt **Setting**: haematology clinic

Bahnasawy 2017 *(Continued)*

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Notes	Sample size calculation not reported Drug-related outcomes do not have any comparable data reported. Only outcomes with comparable data reported are SF levels and health-related QoL.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was a prospective, randomized, controlled study. It was conducted on pediatric BTM patients admitted to the Pediatric Hematology Clinic". Stratified randomisation was used considering the iron chelation therapy as the stratification factor. Judgement comment: no description of how randomisation was done or by whom
Allocation concealment (selection bias)	Unclear risk	The control group (n = 24) received standard medical care by a physician while the intervention group received standard medical care plus clinical pharmacist-provided services Judgement comment: no description of how participants were allocated to the pharmacist intervention or standard care
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Judgement comment: not possible to blind a pharmacist intervention versus no pharmacist intervention
Blinding of outcome assessment (detection bias) All outcomes except mortality	High risk	Judgement comment: no indication that outcome assessors were different from pharmacists who implemented the intervention. Also most outcomes were reported only in the intervention group except for ferritin levels and health-related QoL
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: all drug-related outcomes were only reported in the intervention group including adherence - no comparative data available. Multiple interventions in small number of participants.
Selective reporting (reporting bias)	High risk	Judgement comment: drug-related outcomes reported only in intervention group. No comparative data. The participants within the intervention arm seem to have complex and multiple changes. Difficult to tease out the actual intervention that effected a change.
Other bias	Unclear risk	Judgement comment: small sample size and only report intervention group

Calvaruso 2014

Study characteristics	
Methods	**Study design**: multicentre RCT **Study grouping**: parallel-group **Study duration**: 5 years (with additional 5-year follow-up)
Participants	**Baseline characteristics** No baseline differences noted between groups **Overall** • Total # of participants: 60 • Sex N (%): 30 (50%) female; 30 (50%) male • No other overall characteristics reported **DFP** • Total # of participants: 30 • Age (mean (SD)): 36.4 (13.9) years • Sex N (%): 14 (46.67%) female; 16 (53.33%) male • Sickle cell genotype N (%): NR • Thalassaemia genotype N (%): N/A • Baseline ferritin levels (ng/mL) (mean (SD)): 1440.14 (712.7) • Previous iron chelation: NR • Duration of any iron chelation: NR • LIC (mg/g): NR • Splenectomy (%): 45.4% • Quality of life: NR • Hb (g/l), mean (SD): 89.9 (13.2) **DFO** • Total # of participants: 30 • Age (mean (SD)): 35.8 (11.6) years • Sex N (%): 16 (53.33%) female; 14 (46.67%) male • Sickle cell genotype N (%): NR • Thalassaemia genotype N (%): N/A • Baseline ferritin levels (ng/mL) (mean (SD)): 1726.03 (694.01) • Previous iron chelation: NR • Duration of any iron chelation: NR • LIC (mg/g): NR • Splenectomy (%): 70.6% • Quality of life: NR • Hb (g/l), mean (SD): 86.5 (9.9) **Inclusion criteria** • People with SCD with a serum ferritin concentration between 800 and 3000 ng/mL • Over 13 years of age **Exclusion criteria** • Known intolerance to one of the trial treatments • Platelet count b100,000/µL or leucocyte count b3000/µL • Severe liver damage as indicated by Child-Pugh C grade classification

Calvaruso 2014 *(Continued)*

- Sepsis at entry
- Overt heart failure

Interventions	**DFPintervention** • DFP 75 mg/kg/day, divided into 3 oral daily doses for 7 days/week **DFO intervention** • DFO 50 mg/kg per day by subcutaneous infusion (8 to 10 hours) for 5 days/week
Outcomes	All-cause mortality (at 5 years) Compliance Costs Liver damage (unclear time point, defined as twice normal ALT) Adverse events reported (not SAEs)
Identification	**Sponsorship source**: trial was performed on behalf of the Italian Society for the Study of Thalassemia and Hemoglobinopathies (SoSTE) (http://www.soste.org) **Country**: Italy **Setting**: outpatient. Multicentre: 9 centres in Italy with one co-ordinating centre (A.O.V. Cervello, U.O.C. di Ematologia II, Palermo, Italy) **Author's name**: Giusi Calvaruso (corresponding author: Prof A Maggio) **Institution**: Unita'Operativa Complessa Ematologia II, A.O.R. Villa Sofia–V. Cervello, Palermo, Italy **Email**: md.amaggio@gmail.it (corresponding author) **Address**: U.O.C. “Ematologia II, A.O. R.Villa Sofia–V. Cervello”, Via Trabucco n°180, 90143 Palermo, Italy Fax: +39 0916802895 **Comments**: Incorrectly reported trial registration number as NCT00733811, though this is a different study design (different intervention and comparison), though from the same author group. Study conducted between 30 January 2001 and 30 January 2006
Notes	Incorrectly reported trial registration number as NCT00733811, though this is a different study design (different intervention and comparison), though from the same author group (Maggio 2009).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization sequence was based on a computer randomized list in permuted blocks of 10 with a 1:1 ratio"
Allocation concealment (selection bias)	Low risk	Centralised system: "ensure allocation concealment, treatment was assigned by telephone contact from the coordinating center. The sequence was concealed until interventions were assigned"
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	"The trial was a 5-year multicenter randomized open-label trial with blinded data management and data analyses, to assess whether either treatment was superior to the other... A double-blinded design was not considered to be possible because of the sc administration of DFO." High risk of bias due to open-label design.

Calvaruso 2014 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes except mortality	Low risk	"The trial was a 5-year multicenter randomized open-label trial with blinded data management and data analyses, to assess whether either treatment was superior to the other..." "All outcome assessments were coded by physicians blinded to the trial treatment."
Incomplete outcome data (attrition bias) All outcomes	High risk	Although the authors state that there were no participants lost to follow-up there appears to be a significant reduction in both arms in the number of participants taking the allocated intervention. By year 5 there were only 7/30 taking the allocated intervention in the DFP arm and 14/30 taking the allocated intervention in the DFO arm.
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration to compare outcomes reported. Cannot refer to trial registration as it has been linked to an incorrect trial registration number.
Other bias	Unclear risk	Incorrect trial registration reported (NCT00733811) - may indicate other incorrect reporting (inclusion/exclusion criteria, dates, ethics approval, etc). No apparent baseline imbalance. No apparent conflicts of interest: "The investigators initiated, carried out, and controlled the trial, which was conducted without the influence of the sponsor".

Calvaruso 2015

Study characteristics	
Methods	**Study design**: RCT **Study grouping**: parallel-group This trial was designed as a 5-year, multicentre, randomised, open-label trial with blinded data management and data analyses to evaluate whether the DFP treatment is superior to the DFO treatment Follow-up after trial. An additional 5 years of follow-up after the end of the trial was planned to collect data on the survival, cause of death and chelation treatment of this cohort of participants. During this period, the participants were allowed to change their chelation treatment
Participants	**Baseline characteristics** **DFP** • Total # of participants: 47 • Age: mean (SD): 41.3 (14.8) • Sex n (%): F: 24 (50) • Ethnicity: not reported • Thalassaemia genotype (%): thalassaemia intermedia 100% • Baseline ferritin levels (ng/mL) median (IQR): 1221 (743) • Age at initiation of DFO years: mean (SD): 29.9 (16.8) • LIC (mg/g/dw) median (IQR): 3800 (2800) • Splenectomy n (%): 42 (89.3) • QoL: mean (SD): not reported • Hb, g/L mean (SD): 88 (10) **DFO** • Total # of participants: 41 • Age: mean (SD): 41.2 (14.3)

Calvaruso 2015 *(Continued)*

- Sex n (%): F: 23 (51.1)
- Ethnicity: not reported
- Thalassaemia genotype (%): thalassaemia intermedia 100%
- Baseline ferritin levels (ng/mL) (median (IQR)): 1122 (910)
- Age at initiation of DFO years: mean (SD): 29.6 (17.4)
- LIC (mg/g/dw) median (IQR): 3800 (4668)
- Splenectomy n (%): 35 (77.7)
- QoL: mean (SD): not reported
- Hb, g/L mean (SD): 89 (12)

Inclusion criteria: people with thalassaemia intermedia (based on clinical and molecular criteria), SF between 800 and 3000 µg/L, 13 years of age, consent from patient or parent or guardian (if 13 to 18)

Exclusion criteria: known intolerance to treatment, platelet count < 100 × 10^9/L, white cell count of < 3 × 10^9/L, severe liver damage, sepsis or heart failure (or both)

Pretreatment: none of the participants in the DFP group and 8 in the DFO group withdrew from the trial. 1 participant in the DFP group and 3 in the DFO group changed their chelation therapy (P value = 0.357)

If the participants were treated with a subcutaneous administration of DFO (30 to 50 mg/kg per day, 8 to 12 hours for 5 days a week) before inclusion in the trial, a DFO washout was executed for 1 week before randomisation. The minimum number of participants required for each treatment group was calculated, assuming equal allocation under the hypothesis of equality between the 2 treatment groups at each point during the course. The recommended number of participants was 30.

One participant in the DFP group and 3 in the DFO group changed their chelation therapy

Interventions	**DFP** • DFP (Apotex; Toronto, ON, Canada) administered at 75 mg/kg/day, divided into 3 oral daily doses for 7 days/week **DFO** • DFO (BiofuturaPharma, Omezia, Italy), administered by subcutaneous infusion (8 to 10 hours) at 50 mg/kg per day for 5 days/week Treatment failure was defined as an increase in the SF level to greater than 1000 lg/L from baseline, confirmed by at least 2 consecutive determinations. Participants who failed were switched to the alternative treatment and followed until the end of the trial. The criteria for a dosage reduction to 50 mg/kg of DFP per day were arthralgia and nausea, and the criterion for a reduction to 30 mg/kg of DFO per day was a local reaction at the site of infusion. Both treatments were reduced if the ferritin levels for 2 consecutive determinations were less than 400 lg/L. The treatment was resumed when the ferritin levels were greater than 700 lg/L for at least 2 determinations
Outcomes	**Adherence** to iron chelation therapy rates **Compliance** was assessed by counting the number of DFP pills in each returned bag and by assessing the number of infusions of DFO registered on the electronic pump **Trial-reported outcomes** 1. The primary endpoint was treatment effectiveness, evaluated as the mean change in the SF level over the 5-year period. This type of evaluation strengthened the power of the test for the sample size calculation compared with the standard. 2. The secondary endpoints were safety and survival analysis after 5 years
Identification	**Sponsorship source**: contract grant sponsor: Franco and Piera Cutino Foundation **Country**: Italy (17 centres)

Calvaruso 2015 *(Continued)*

Setting: haematology and thalassaemia clinical centres at institutions

Recruitment: January 2001 to January 2006

Trial registration: NCT00733811 *Incorrectly reported trial registration number as NCT00733811, though this is a different study design (different intervention and comparison), though from the same author group (Maggio 2009)*

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Notes	Sample size calculation reported for primary outcome **Notes**: 9 participants changed from DFP therapy 5 to DFO 2 to none 1 to DFX 1 to DFP-DFO 6 participants changed from DFO therapy 4 to DFP 1 to DFX 1 to DFP-DFO

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization sequence was based on a computer- randomized list arranged in permuted blocks of 10 with a 1:1 ratio."
Allocation concealment (selection bias)	Low risk	To ensure for allocation concealment, treatments were assigned by telephone contact from the coordinating centre. The sequence was concealed until the interventions were assigned. Randomisation was performed for each consecutive patient after verification of the exclusion criteria.
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Quote: "open-label trial" Judgement comment: 1 of 2 arms was Desferal pump infusers; participants would know. Participants on DFO attended for weekly blood tests.
Blinding of outcome assessment (detection bias) All outcomes except mortality	Low risk	Quote: "with blinded data management and data analysis"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up for 5-year trial
Selective reporting (reporting bias)	Low risk	All outcomes reported

Calvaruso 2015 *(Continued)*

Other bias	Unclear risk	Unclear how participant variation relating to SF levels may have had effect on results. Although all outcomes were reported for the 5-year trial, in the 5 years of follow-up only mortality was reported.

Elalfy 2015

Study characteristics	
Methods	**Study design**: RCT in 2 treatment centres **Study grouping**: parallel-group **Study duration**: 1 year
Participants	**Baseline characteristics** **Group A: DFP/DFO** • Total # of participants: 48 • Age: mean (SD): 15.25 (2.31) • Sex: male n (%): 30 (62.5) • Ethnicity: not reported • Thalassaemia genotype N (%): not stated; all participants appear to have β-thalassaemia major • Baseline ferritin levels (ng/mL): mean (SD): 4379.07 (895.00); range 3632 to 6210 • Duration of any iron chelation (years): mean (SD): 8.71 (2.7) • LIC (mg/g): mean (SD): 12.69 (2.23); range: 12.69 to 2.23 • Splenectomy n (%): 21 (43.7) • QoL mean (SD): 63.09 (5.77) • Hb, g/L mean (SD): 81.1 (3.3) • Mean geometric cardiac T2*(ms): mean (SD): 16.32 (1.82); range: 14.9 to 18.2 **Group B: DFP/DFX** • Total # of participants: 48 • Age: mean (SD): 14.05 (2.21) • Sex: male n (%): 32 (66.6) • Ethnicity: not reported • Thalassaemia genotype N (%): not stated all participants appear to have β-thalassaemia major • Baseline ferritin levels (ng/mL) mean (SD): 4289.19 (866.21); range: 3451 to 7122 • Duration of any iron chelation (years): mean (SD): 8.95 (2.8) • LIC (mg/g): mean (SD): 12.52 (2.28); range: 9.82 to 15.12 • Splenectomy n (%): 20 (41.6) • QoL mean (SD): 63.38 (5.98) • Hb, g/L mean (SD): 79 (3.8) • Mean geometric cardiac T2*(ms): mean (SD):16.59 (1.85); range: 15.7 to 18.9 **Inclusion criteria**: people with β-thalassaemia major aged 10 to 18 years with severe iron overload defined as: ferritin > 2500 µg/L on maximum tolerated dose of a single iron chelator with up trend of ferritin over the last 12 months prior to the study. People with LIC more than 7 mg/g by MRI R2* and mean cardiac T2* less than 20 and more than 6 ms calculated as geometric mean without clinical symptoms of cardiac dysfunction (shortness of breath at rest or exertion, orthopnoea, exercise intolerance, lower extremity oedema, arrhythmias). Adequacy of prior chelation defined as taking 75% of the calculated dose/month on maximum tolerated dose with upward ferritin trend.

Elalfy 2015 *(Continued)*

	Exclusion criteria: past history of agranulocytosis, clinically significant GI or renal disease, clinical cardiac disease, or with LVEF < 50% on baseline echocardiography; evidence of active hepatitis or serum transaminases > 3 times above ULN or renal impairment (serum creatinine > ULN), participation in a previous investigational drug study within the 30 days preceding screening, known allergy to DFX, DFP, and DFO. **Pre-treatment**: baseline difference in mean Hb (P 0.004)
Interventions	**DFP/DFO** • DFP 75 mg/kg/day divided into 2 doses taken orally at 8 a.m. and 3 p.m. for 7 days (with 6 to 8 hours interval between the 2 doses) combined with DFO 40 mg/kg/day by subcutaneous infusion over 10 hours starting at 10 p.m. for 6 days/week **DFP/DFX** • DFP 75 mg/kg/day, divided into 2 doses taken orally at 8 a.m. and 3 p.m. combined with DFX 30 mg/kg/day taken orally at 10 p.m. for 7 days/week To achieve an acceptable treatment washout, chelation therapy was withdrawn for 2 weeks before randomisation, after verifying inclusion and exclusion criteria. The transfusion regimen aimed to maintain the participants pre-transfusion Hb ≥ 80 g/L by receiving approximately 15 mL/kg packed RBCs every 3 to 4 weeks.
Outcomes	**Adherence** to iron chelation therapy rates Compliance was evaluated by counting of returned tablets for the oral chelators and of the vials for DFO. The percentage of actual dose that participants had taken in relation to the total prescribed dose was calculated. **Trial-reported outcomes** 1. % change in SF (from baseline to the end of trial) 2. % change in LIC (from baseline to the end of trial) 3. % change in cardiac MRI (from baseline to the end of trial) 4. SAEs and AEs (safety assessment) 5. Compliance 6. Satisfaction 7. QoL
Identification	**Sponsorship source**: Ain Shams University **Country**: Egypt and Oman **Setting**: thalassaemia treatment centres (Ain Shams University, Egypt and Sultan Qaboos University Hospital, Oman) **Comments**: Government Clinical Trial NCT01511848 **Authors name:** Amira Abdel Moneam Adly **Institution**: Department of Pediatrics, Ain Shams University, Cairo, Egypt **Email**: amiradiabetes@yahoo.com **Address**: 6 A ElSheshini street, Shoubra, Soudia buildings, Cairo, Egypt
Notes	The chelation regimens in the last year prior to the trial were daily DFX (14 participants), daily DFP (29 participants) and DFP 4 days/week alternating with subcutaneous DFO 3 days/week (53 participants)

Elalfy 2015 *(Continued)*

	Sample size calculation reported Author contacted for additional info on SF 36 mean (SD) at 6 months and end of trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation sequence was based on a computer randomised list in permuted blocks of 10 with a 1: 1 ratio, generated at both University of Ain Shams and Sultan Qaboos"
Allocation concealment (selection bias)	Low risk	Quote: "To ensure no allocation bias, treatment group was assigned by telephone contact from the coordinating center in Ain Shams"
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Oral versus subcutaneous medication therefore participants would be aware to which medication arm they had been randomised
Blinding of outcome assessment (detection bias) All outcomes except mortality	Low risk	Quote: "open-label study with blinded data management and data analyses"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement comment: treatment was started within the following 24 hours, and all the included participants continued until the end of study with no participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Judgement comment: provide only P values for patient satisfaction, satisfaction with ICT self-reported satisfaction and all 'significantly' higher in group B; no actual end of trial data provided (mean (SD)). All outcomes are reported.
Other bias	Unclear risk	Judgement comment: it is not clear how the investigators would have known that infections, GI disorders or skin disorders were not related to the drug therapies

El Beshlawy 2008

Study characteristics

Methods	**Study design**: single-centre RCT **Study grouping**: parallel-group, follow-up for 54 weeks
Participants	**Baseline characteristics** **DFP/DFO** • Total # of participants: 18 • Age (mean (SD): 11.0 (4.9) • Sex: F: 10; M: 8 • Ethnicity: not reported • Thalassaemia genotype N (%) : β-thalassaemia major: 100% • Baseline ferritin levels (ug/mL) (mean (SD) (range)): 2865 (983) (1500 to 4800)

El Beshlawy 2008 *(Continued)*

- Previous iron chelation: not reported
- LIC (mg/g) mean (SD) (range): 17.1 (9.1) (4.9 to 33.6) N = 16
- Splenectomy n (%): 11 (61)
- QoL mean (SD): not reported
- Hb, g/L (mean (SD) (range): 68 (5) (55 to 75)

DFP

- Total # of participants: N = 18
- Age (mean (SD) (range)): 10.8 (5.1) (5 to 26)
- Sex: F: 6; M: 12
- Ethnicity: not reported
- Thalassaemia genotype N (%) : β-thalassaemia major: 100%
- Baseline ferritin levels (ug/mL) (mean (SD) (range)): 2926 (1107) (1560 to 5000)
- Previous iron chelation: not reported
- LIC (mg/g) (mean (SD) (range)): 15.8 (7.1) (2.3 to 29.3) N = 17
- Splenectomy n (%): 9 (50)
- QoL mean (SD): not reported
- Hb, g/L mean (SD) (range): 69 (6) (58 to 80)

DFO

- Total # of participants: N = 20
- Age (mean (SD) (range)): 13.1 (5.9) (5.5 to 24)
- Sex: F: 9; M: 11
- Ethnicity: not reported
- Sickle cell genotype N (%) - not applicable:
- Thalassaemia genotype N (%): β-thalassaemia major: 100%
- Baseline ferritin levels (ug/mL) (mean (SD)(range)): 2 838 (967) (1500 to 4300)
- Previous iron chelation: not reported
- LIC (mg/g) mean (SD) (range): 22.5 (10.1) (6.0 to 41.7) N = 15
- Splenectomy n (%): 10 (50)
- QoL mean (SD): not reported
- Hb, g/L mean (SD) (range): 69 (5) (60 to 80)

Inclusion criteria: males or females with thalassaemia major attending the Hematology Clinic at Cairo University Children Hospital; participants had to be iron overloaded with transfusion dependency and older than 4 years of age

Exclusion criteria: known to have DFP or DFO toxicity; neutrophil count less than 1.5×10^9/L; platelet count less than 100×10^9/L; renal or hepatic insufficiency; decompensated heart failure; without contraceptive precaution; pregnant or nursing

Interventions	**DFP/DFO** • DFP + DFO (dose 60 to 83 mg/kg/day and DFO 23 to 50 mg/kg per dose) DFP 7 days and DFO over 8 hours 2 days/week **DFP** • DFP only (dose 60 to 83 mg/kg/day) 7 days per week **DFO** • DFO 23 to 50 mg kg/day monotherapy for 5 days/week
Outcomes	**Adherence** to iron chelation therapy rates

El Beshlawy 2008 *(Continued)*

	Compliance was assessed by performing a drug accounting at each patient visit by counting the returned empty blisters of DFP and used vials of DFO **Trial-reported outcomes** 1. Incidence of chelation therapy-related SAEs (reported in AEs) 2. Iron overload defined by ferritin over 1000 µg/L and/or clinical symptoms and/or signs of iron overload and/or need for medically indicated additional or change in chelation therapy (mean ferritin levels extrapolated from graph - no SD provided) 3. Other AEs related to iron chelation (in this trial participants with an event are reported. 1 person could experience more than 1 event) 4. LIC mg/g dry weight (change from baseline (extrapolated from graph least squares means/lower and upper value))
Identification	**Sponsorship source** **Country**: Egypt **Setting**: Haematology Clinic at Cairo University Children Hospital, Egypt **Comments**: 2 authors from Lipomed (DFP): C. Manz: C. Tarabishi Clinical Research Development, Lipomed AG, Arlesheim, Switzerland **Authors name**: A. El-Beshlawy **Institution**: Faculty of Medicine, Cairo University **Email**: amalelbeshlawy@yahoo.com **Address**: Faculty of Medicine, Cairo University, 32 Falaky Street, Bab El-Louk, Cairo, Egypt
Notes	Sample size calculation reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement comment: no description of how randomisation was accomplished: the participants were randomly assigned into 1 of 3 treatment arms
Allocation concealment (selection bias)	Unclear risk	Judgement comment: no description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	No mention of blinding - since DFO is an injection and DFP is oral likely participants and personnel not blinded
Blinding of outcome assessment (detection bias) All outcomes except mortality	Unclear risk	Judgement comment: no blinding mentioned
Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement comment: a total of 10 participants dropped out of the trial as a result of several complications. Only 56 participants completed 54 weeks of

El Beshlawy 2008 *(Continued)*

		treatment. Evaluation of LIC could not be done in another 8 participants. Reports on per protocol participants.
Selective reporting (reporting bias)	High risk	Compliance not reported as number or percentage of participants compliant throughout trial: "Four patients, all treated with DFO-based regimen, were excluded from the study due to lack of compliance. Compliance was otherwise excellent during the entire study. The majority of patients had no problems with the intake and swallowing of the DFP tablets. By contrast, 80% of patients in the combination arm and 76% of patients in the DFO monotherapy arm complained about difficulties in the parenteral use of DFO or problems to insert a needle". SF and LIC are partially reported in charts and no actual numbers are provided in the text. Also, the focus on UIE over LIC and SF measures is misleading as DFP is known to have a higher UIE, but this can be highly variable over multiple measurements. LIC is the gold standard and there was no difference in this outcome between groups.
Other bias	Unclear risk	There was a higher incidence of AEs in the combined group and the DFP group versus the DFO group

Galanello 2006a

Study characteristics	
Methods	**Study Design**: 2-arm parallel RCT conducted in Italy and Greece **Number of centres**: multicentre (3 centres) **Duration of treatment**: 12 months **Follow-up**: not stated
Participants	**DFP/DFO** • Total # of participants: randomised 30, analysed 29 (withdrawn after 2 days on trial before taking DFP) • Age (mean (SD): 19.8 (6.1) years • Sex: F: 13; M: 16 • Ethnicity: not reported • Thalassaemia genotype N (%) : β-thalassaemia major: 100% • Baseline ferritin levels (ug/mL) mean (SD): 2048 (685) • Previous iron chelation: not reported • LIC (mg/g) mean (SD) (range): 17.1 (9.1) (4.9 to 33.6) N = 16 • Splenectomy n (%): 11 (61) • QoL mean (SD): not reported • Hb, g/L mean (SD) (range): 68 (5) (55 to 75) **DFO** • Total # of participants: randomised 30, analysed 30 • Age (mean (SD)): 18.7 (4.8) years • Sex: F: 18; M: 12 • Ethnicity: not reported • Thalassaemia genotype N (%) : β-thalassaemia major: 100% • Baseline ferritin levels (ug/mL) (mean (SD): 2257 (748) • Previous iron chelation: not reported • LIC (mg/g) mean (SD) (range): 17.1 (9.1) (4.9 to 33.6) N = 16 • Splenectomy n (%): 11 (61) • QoL mean (SD): not reported • Hb, gL mean (SD) (range): 68 (5) (55 to 75)

Galanello 2006a *(Continued)*

	Inclusion criteria: participants were 10 years or older with a diagnosis of thalassaemia major undergoing iron chelation therapy with subcutaneous DFO, with a SF value between 1000 and 4000 µg/L over the previous year. **Exclusion criteria**: not reported
Interventions	**DFO**: 20 to 60 mg/kg/day subcutaneously on 5 to 7 days a week (mean (SD) dose at baseline: 34.8 (8.9) mg/kg/day and at end of trial: 37.8 (8.9) mg/kg/day) **DFO/DFP**: DFO 20 to 60 mg/kg/day subcutaneously on 2 days a week (mean (SD) dose DFO for the 29 participants who completed the trial at baseline: 36.0 (5.8) mg/kg/day and at end of trial: 33.3 (6.64) mg/kg/day) with DFP 25 mg/kg/body weight 3 x daily for 5 days a week
Outcomes	**Adherence** see compliance below **Trial-reported outcomes** 1. SF change at 1 year 2. LIC (measured by SQUID) change at 1 year 3. ALT 4. FBC 5. Zinc levels 6. AEs 7. Participant compliance: compliance with DFP was assessed by pill counts, diary cards and an electronic cap that recorded the time and date of each opening of the tablet container. Compliance with DFO was assessed by diary cards, weekly physical examination of infusion sites, and by the Crono™ infusion pump that recorded the number of completed infusions Primary outcome: not identified
Identification	Source of funding: Apotex Research Inc, Toronto, Canada. The last author of the study is an Apotex employee.
Notes	The trial inferred that participants had previously received DFO treatment but no details as to dose, schedule or duration were reported Sample size calculation not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors did not report any information about how randomisation was undertaken
Allocation concealment (selection bias)	Unclear risk	The authors did not report any information about how treatment allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	Unclear risk	The authors did not report any information as to whether participants, personnel or outcome assessors were blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes except mortality	Unclear risk	The authors did not report any information as to whether outcome assessors were blinded to treatment allocation
Incomplete outcome data (attrition bias)	Low risk	Although 1 participant in the treatment group was withdrawn due to intolerance to DFP, this is unlikely to effect the findings of the trial

Galanello 2006a *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Compliance to DFP was pre-specified as an outcome but was not measured or reported in the manuscript
Other bias	Low risk	The trial appears to be free of other sources of bias

Gharaati 2019

Study characteristics	
Methods	**Study design**: quasi experimental study (non-RCT), single-centre **Study duration**: "in 2017 from May to January"
Participants	**Baseline characteristics** **Group differences** There appeared to be significant differences at baseline between the 2 groups including knowledge etc. within the questionnaire, use of chelation therapy. In the intervention group 22% (10) used only oral chelation therapy, but only 9% (4) used only oral chelation therapy in the control group. **Educational intervention** • Total # of participants: 46 • Age (mean (SD)): 20.11 (4.8) years • Sex N (%): 23 (50%) female; 23 (50%) male • Splenectomy N (%): 8 (17.4%) **Standard care (as defined in the study)** • Total # of participants: 45 • Age (mean (SD)): 20.56 (5.8) years • Sex N (%): 25 (55.6%) female; 20 (44.4%) male • Splenectomy N (%): 15 (33.3%) **Inclusion criteria** • People with thalassaemia major who visited Hazrat Abolfazl Hospital in Minab • Willingness to take up phone-mediated education • Having an active medical file in the thalassaemia ward of the hospital and regular visits to the hospital to receive the required services • 13+ years of age • Having a mobile phone either of one's own or their family • No mental or behavioural disorder • No hearing or speech problems **Exclusion criteria** • Reluctance to take part in the research • Attendance of fewer than 3 sessions in the educational programme • A history of participating in a similar educational programme
Interventions	**Educational intervention** The phone-mediated educational intervention occurred through 6 calls lasting 15 to 18 minutes within 1 month. The calls were made at the participants' convenience from 8 am to 8 pm. The topic of the first

Gharaati 2019 *(Continued)*

	call was familiarity with the disease. The topic of the second call was significance of taking chelation drugs. The third phone call was about the side effects of thalassaemia while the fourth call addressed nutrition and thalassaemia. The fifth phone call dealt with physical activity and the disease while the sixth call was concerned with smoking. The content of each call after greeting was an examination of the participant's knowledge of the topic and the source of information. Then the educational content was posed in a question and answer format. **Control** Standard care (as defined in the study)
Outcomes	The following outcomes were measured (but not reported in the review) • Knowledge • Attitude • Nutritional behaviours • Use of chelation therapy • Blood injection • Referral to specialist • Physical activity • Smoking • Performance
Identification	**Sponsorship source**: Hormozgan University of medical sciences **Country**: Iran **Setting**: community (phone calls at patient convenience) **Author name**: Teamur Aghamolaei **Institution**: Hormozgan University of Medical Sciences, Bandar Abbas **Email**: teaghamolaei@gmail.com **Address**: Department of Social Determinants in Health Promotion Research Center, Faculty of Health, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
Notes	Due to severe baseline confounding, we assessed the risk of bias using ROBINS-I as critical, and so are unable to use the data

Hassan 2016

Study characteristics	
Methods	**Study design**: single-centre RCT **Study grouping**: parallel-group **Trial duration:** September 2014 to September 2015
Participants	**Baseline characteristics** **DFX** • Total # of participants: 30 • Age mean (SD): 8.9 (2.2) • Sex male/female: 9/21

Hassan 2016 *(Continued)*

- Thalassaemia genotype (%): β-thalassaemia major: 100%
- Baseline ferritin levels (ng/mL) median (range): 3216 (2100 to 5862)
- Previous iron chelation: 100%
- Duration of any iron chelation: not reported
- LIC (mg/g): not reported
- Splenectomy n (%): 4 (13.3)
- QoL mean (SD): not reported
- Hb, g/dL mean (SD): 85 (12)

DFO

- Total # of participants: 30
- Age mean (SD): 9.7 (1.9)
- Sex male/female: 10/20
- Thalassaemia genotype (%): β-thalassaemia major: 100%
- Baseline ferritin levels (ng/mL) median (range): 2773 (1980 to 4884)
- Previous iron chelation: 100%
- Duration of any iron chelation: not reported
- LIC (mg/g): not reported
- Splenectomy n (%): 17 (56.7)
- QoL mean (SD): not reported
- Hb, g/dL mean (SD): 7.9 (2.4)

Inclusion criteria: transfusion-dependent β-thalassaemia major, ages were ≥ 6 years, and they had SF levels greater than 1500 µg/L and were on irregular subcutaneous DFO chelation therapy

Exclusion criteria: serum creatinine above the upper age-related normal range, significant proteinuria (urinary protein/creatinine ratio 1.0 in a non–first-void urine sample at baseline), elevated ALT more than 3-fold of the ULN, GI diseases, clinically relevant auditory and/or ocular toxicity related to iron chelation therapy, cardiac disease, and/or SAEs with DFO or DFX, and absolute heutrophilic count 1500/mm^3 or platelet count 100,000/mm^3

Pre-treatment: significant difference between the 2 groups with participants having splenectomy 4 in DFX group compared to 17 in DFO group (P = 0.001), hepatitis C status 2 in DFX group compared to 11 in DFO group (P = 0.005) and baseline ALT baseline mean of 28.2 in the DFX group compared to 46.1 in the DFO group (P = 0.001)

Interventions	**DFX** • DFX was administered orally as a single daily dose of 20 to 40 mg/kg/day on an empty stomach after dissolution in water, apple juice or orange juice to assure adequate bioavailability. Starting dose of DFX was individualised based on the frequency of blood transfusions **DFO** • DFO was administered at 20 to 50 mg/kg/day via subcutaneous infusion over 8 to 10 hours, 5 days per week 7-day washout phase
Outcomes	**Adherence** to iron chelation therapy rates During the study, we kept records of all dosages administered, all study medications that were dispensed and returned, and intervals between visits to determine compliance with the treatment. The patients' parents were instructed to contact the investigator if the patients were unable to take the study drug as prescribed. **Trial-reported outcomes** 1. Decrease in the SF level to < 1500 µg/L

Hassan 2016 *(Continued)*

	2. Safety of the drugs that were used
Identification	**Sponsorship source**: not stated **Country**: Egypt **Setting**: outpatient paediatric haematology clinic Al- Hussein University Hospital, Al-Azhar University, Cairo, Egypt **Comments**: no conflict of interest **Authors name**: Dr Omar Atef Tolba **Institution**: Cairo University Children's Hospital **Email**: omartolba80@yahoo.com **Address**: Dr Omar Atef Tolba, Cairo University Children's Hospital, Department of Pediatrics, Cairo University, Egypt. Tel: +201222101717, +20233025539, Fax: +20233025539 There is no conflict of interest declared
Notes	Sample size calculation not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the patients were randomized in a 1:1 ratio based on permuted blocks to receive deferasirox (DFX) or deferoxamine (DFO) for one year." Judgement comment: it is unclear risk as there is imbalance in the groups on several variables
Allocation concealment (selection bias)	Unclear risk	Judgement comment: allocation concealment not described and imbalance between groups
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Judgement comment: oral tablet versus subcutaneous infusion - unable to blind participants or personnel
Blinding of outcome assessment (detection bias) All outcomes except mortality	High risk	Quote: "During the study, we kept records of all dosages administered, all study medications that were dispensed and returned, and intervals between visits to determine compliance with the treatment." Judgement comment: does not state if outcome assessors were blinded. Assessors would be aware of the treatment participants were on.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "no discontinuation of drugs or drop-out of follow-up occurred."
Selective reporting (reporting bias)	High risk	Quote: "Post-treatment levels of ALT and AST were significantly higher in the DFO group (p = 0.022, p = 0.020, respectively), both drugs have comparable safety profiles, as the adverse effects noted did not reach clinical significance or lead to discontinuation of treatment with either agent. In the light of the comparable efficacy and safety of both agents for the reduction of iron overload, as was reported in the monotherapy of patients with transfusion-dependent thalassaemia (31, 32), the oral preparation merits convenience and there-

Hassan 2016 *(Continued)*

		fore patient compliance and adherence to treatment regimen that needs to be taken on a long-term basis." "The oral DFX is recommended due to more convenience to assure adherence to treatment regimen." Judgement comment: the data within this trial do not provide evidence that DFX assures adherence. Pre-treatment ALT, AST were also higher in the DFO group - and also reflects imbalance in randomisation. Most outcomes vaguely reported (i.e. compliance - not percentages even though did a count and closely monitored). Also, not clear if all drug-related AEs reported (i.e. agranulocytosis). Further the evidence is uncertain from this trial that both drugs of comparable efficacy and safety.
Other bias	Unclear risk	Small trial N = 60 and short-term follow-up. Sample size calculation not reported, and single-centre trial.

Kwiatkowski 2021

Study characteristics	
Methods	**Study design**: single-centre, open-label RCT (randomised 2:1 (DFP: DFO)) **Study grouping**: parallel-group **Study duration**: 12 months
Participants	**Baseline characteristics** No group differences noted Overall • Total # of participants: 228 • Age (mean (SD)): 16.9 (9.6) years • Sex N (%): 107 (46.9%) female, 121 (53.1%) male • Previous iron chelation: 122/228 DFP intervention • Total # of participants: 152 • Age (mean (SD)): 16.9 (10.2) years • Sex N (%): 69 (45.4%) female, 83 (54.6%) male • Sickle cell genotype N (%): NR • Thalassaemia genotype N (%): N/A • Baseline ferritin levels (ng/mL) (mean (SD)): 4114.5 (2385.7) (n = 143) • Previous iron chelation: DFP n = 28; DFO n = 25; DFX n = 38; none n = 74 • Duration of any iron chelation: NR • LIC (mg/g), mean (SD): 16.44 (7.53) (n = 133) • Splenectomy (%): NR • Quality of life: NR • Hb (g/l), mean (SD): NR DFO intervention • Total # of participants: 76 • Age (mean (SD)): 16.9 (8.5) years

Kwiatkowski 2021 *(Continued)*

- Sex N (%): 38 (50%) female, 38 (50%) male
- Sickle cell genotype N (%): NR
- Thalassaemia genotype N (%): N/A
- Baseline ferritin levels (ng/mL) (mean (SD)): 4136.9 (2649.1) (n = 74)
- Previous iron chelation: DFP n = 19; DFO n = 17; DFX n = 17; none n = 32
- Duration of any iron chelation: NR
- LIC (mg/g), mean (SD): 15.79 (7.14) (n = 69)
- Splenectomy (%): NR
- Quality of life: NR
- Hb (g/l), mean (SD): NR

Inclusion criteria*

- Male or female ≥ 2 years of age
- SCD confirmed by Hb electrophoresis or more specific tests, or other conditions with iron overload from repeated blood transfusions (see exclusion criteria for exceptions)
- Baseline LIC > 7 mg/g dw (measured by MRI)
- Received no less than 20 transfusions of RBCs
- Received at least 1 transfusion per year in the last 2 years and expected to have a continuing requirement (based on Investigator's judgement) during the duration of the trial

Exclusion criteria*

- Thalassaemia syndromes
- Myelodysplastic syndrome (MDS) or myelofibrosis
- Diamond Blackfan anaemia
- Primary bone marrow failure
- Baseline LIC > 30 mg/g dw (measured by MRI)
- Unable or unwilling to undergo a 7-day washout period if currently being treated with DFP or DFO or DFX
- Previous discontinuation of treatment with DFP or DFO due to AEs
- History or presence of hypersensitivity or idiosyncratic reaction to DFP or DFO
- Treated with hydroxyurea within 30 days
- History of malignancy
- Evidence of abnormal liver function (serum ALT level(s) > 5 times ULN at screening or creatinine levels > 2 times ULN at screening)
- Serious, unstable illness, as judged by the Investigator, during the past 3 months before screening/baseline visit including but not limited to: hepatic, renal, gastro-enterologic, respiratory, cardiovascular, endocrinologic, neurologic or immunologic disease
- Clinically significant abnormal 12-lead ECG findings
- Cardiac MRI T2* < 10 ms
- Myocardial infarction, cardiac arrest or cardiac failure within 1 year before screening/baseline visit
- Unable to undergo MRI
- Presence of metallic objects such as artificial joints, inner ear (cochlear) implants, brain aneurysm clips, pacemakers and metallic foreign bodies in the eye or other body areas that would prevent use of MRI imaging

*taken from trial registration entry

Interventions	**DFP intervention** • DFP taken orally as 3 doses per day approximately 8 hours apart. Dosage based on body weight and on extent of iron load, for less severe a total daily dosage of DFP 75 mg/kg (25 mg/kg per dose) and for more severe DFP 99 mg/kg (33 mg/kg per dose). **DFO intervention**

Kwiatkowski 2021 *(Continued)*

	DFO administered as a subcutaneous infusion over 8 to 12 hours, 5 to 7 days per week. Dosage based on body weight and on extent of iron load, for less severe a daily dose of DFO 20 mg/kg (children) or 40 mg/kg (adults), for more severe a daily dose of up to DFO 40 mg/kg (children) or 50 mg/kg (adults).
Outcomes	Efficacy endpoints were the changes from baseline in LIC, cardiac iron and SF at month 12 The primary endpoint was based on LIC, and for the demonstration of non-inferiority of DFP to DFO, the upper limit of the 95% CI for the difference between treatments had to be no more than 2 mg/g dw Safety assessments and compliance with study therapy were evaluated monthly. Acceptable compliance was defined as taking 80% to 120% of the prescribed dosage. Outcomes for this review • Adherence • Mortality • HRQoL • SAEs: pain crisis, hepatic sequestration, acute chest syndrome, chelation associated • All SAEs • Other AEs related to iron chelation
Identification	**ClinicalTrials.gov Identifier:** NCT02041299 **First posted:** 22 January 2014 **Results first posted**: 10 August 2021 **Last update posted**: 10 August 2021
Notes	**Sponsorship source**: Chiesi Canada Corp (ApoPharma) **Country**: 8 countries (Brazil, Canada, Egypt, Saudi Arabia, Tunisia, Turkey, UK, USA) **Setting**: outpatient **Author's name**: Janet Kwiatkowski, MD **Institution**: Children's Hospital of Philadelphia, United States **Email**: kwiatkowski@email.chop.edu **Address**: Division of Hematology, The Children's Hospital of Philadelphia, 3401 Civic Center Blvd, Philadelphia, PA 19104, United States **Comments** • Terminated early (sponsor decision): difficulties with additional recruitment as pool of potential participants was exhausted, and sufficient information for determination of study outcome measure was already obtained • QoL data presented as mean (SE), converted to SD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Eligible patients were randomly assigned in a 2:1 ratio to receive either deferiprone or deferoxamine for up to 12 months. Randomization was stratified by disease category (SCD vs other anemias) and transfusional iron input in the 3 months before baseline" From protocol: "A randomization list will be generated for each stratum, assigning study medication to individual randomization numbers in blocks of 6. Treatment assignment and drug allocation will be per-

Kwiatkowski 2021 *(Continued)*

		formed by an Interactive Voice Response System (IVRS)." No information regarding how randomisation list was generated
Allocation concealment (selection bias)	Low risk	"Eligible patients were randomly assigned in a 2:1 ratio to receive either deferiprone or deferoxamine for up to 12 months. Randomization was stratified by disease category (SCD vs other anemias) and transfusional iron input in the 3 months before baseline" "Eligible patients were randomly assigned in a 2:1 ratio to receive either deferiprone or deferoxamine for up to 12 months. Randomization was stratified by disease category (SCD vs other anemias) and transfusional iron input in the 3 months before baseline" From protocol: "A randomization list will be generated for each stratum, assigning study medication to individual randomization numbers in blocks of 6. Treatment assignment and drug allocation will be performed by an Interactive Voice Response System (IVRS)."
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	"multicenter, randomized, open-label study" Open-label study
Blinding of outcome assessment (detection bias) All outcomes except mortality	High risk	Open-label study and no description of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT for safety population. But significant loss to follow up in both groups for other outcomes (deferiprone 46/152 (30%); deferoxamine 18/76 (24%) withdrawn). Planned outcomes reported within clinical trials registration. Methodology of handling missing data may lead to biases. "For all measures, the last-observation-carried-forward method was used to fill in missing data for patients who withdrew early from the study."
Selective reporting (reporting bias)	Low risk	Planned outcomes reported in clinical trial registration. Outcomes listed have been reported.
Other bias	Unclear risk	Trial stopped early, and this may have led to a risk of bias. "Terminated (Difficulties with additional recruitment as pool of potential patients was exhausted, and sufficient information for determination of study outcome measure was already obtained)". No baseline group differences.

Maggio 2009

Study characteristics	
Methods	**Study design**: multicentre RCT **Study grouping**: parallel-group Consecutive thalassaemia major participants (n = 275) were observed at the 25 SoSTE centres from 30 September 2000 to 31 January 2008 9 participants did not meet inclusion criteria and 53 patients declined to participate. The remaining 213 participants were included; 105 and 108 respectively, were randomly allocated to DFP–DFO sequential treatment or DFP alone (Fig 1). None of the participants were lost to follow-up. **Study duration**: 5-year follow-up

Maggio 2009 *(Continued)*

Participants	**Baseline characteristics** **DFP/DFO** • Total # of participants: 105 • Age: mean (SD): 23 (8.0) • Sex: N (%): F: 55 (50.9) • Thalassaemia genotype (%): thalassaemia major (100%) • Baseline ferritin levels (ng/mL): mean (SD): 1727 (669) • Previous iron chelation: N = 105 • Duration of any iron chelation: not stated • LIC (mg/g): mean SD: 4.6 (2.8) • Splenectomy: N (%): 17 (14.0) • QoL mean (SD): not reported • Hb, g/L: mean SD: 99 (10) **DFP** • Total # of participants: N = 108 • Age: mean SD: 23 (7.8) • Sex: N (%): F: 66 (61.1) • Thalassaemia genotype (%): thalassaemia major (100%) • Baseline ferritin levels (ng/mL): mean (SD): 1868 (845) • Previous iron chelation: N = 108 • Duration of any iron chelation: not stated • LIC (mg/g): mean (SD): 4.0 (2.3) • Splenectomy: N (%): 15 (12.7) • QoL mean (SD): not reported • Hb, g/L: mean (SD): 98 (10) **Inclusion criteria**: thalassaemia major, SF between 800 and 3000 ug/L over 13 years of age **Exclusion criteria**: known intolerance treatment, platelet count 100 x 109/L or leucocyte count 3.0 x 109/L, severe liver damage, heart failure
Interventions	**DFP/DFO** • DFP 75 mg/kg, divided into 3 oral daily doses, for 4 days/week and DFO subcutaneous infusion (8 to 12 hours) at 50 mg/kg per day for the remaining 3 days/week **DFP** • DFP alone, at the same dosage (75 mg/kg divided into 3 oral daily doses), administered 7 days a week
Outcomes	**Adherence** Compliance was assessed by counting the pills in each returned bag of DFP and by assessing the number of infusions of DFO registered on the electronic pump **Trial-reported outcomes** 1. Difference between multiple observations of SF concentrations during the 5-year treatment. A correlation between LIC and SF levels has previously been shown in a cohort of people with thalassaemia major treated with DFP (Olivieri et al, 1995). 2. Survival analysis 3. AEs 4. Costs

Maggio 2009 *(Continued)*

	5. Multislice-multiecho T2* MRI scan, available since June 2004, was used in a subgroup of participants to evaluate variations in the iron content of the heart and liver during the trial
Identification	**Sponsorship source**: Italian Society for the Study of Thalassaemia and Haemoglobinopathies (SoSTE) **Country**: Italy **Setting**: 25 SoSTE centres in Italy **Comments**: NCT 00733811 **Authors name**: Aurelio Maggio **Institution**: A.O.V. Cervello, U.O.C. di Ematologia **Email**: aureliomaggio@virgilio.it **Address**: A.O.V. Cervello, U.O.C. di Ematologia II, Cervello, Palermo, Italy
Notes	Follow-up was planned for 5 years; however, because of the beneficial effects, in terms of SF levels reduction in the sequential DFP–DFO group, observed after the interim analysis performed on 31 January 2008 the trial was stopped before the planned 5 years of treatment were completed for all participants years but mean (SD) duration of treatment was 2.5 (2.2) and 2.9 (2.1) years for DFP and sequential DFP–DFO groups, respectively Sample size calculation reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization sequence was based on a computer-randomized list in permuted blocks of 10 with a 1:1 ratio" Judgement comment: the randomisation sequence was based on a computer-randomised list in permuted blocks of 10 with a 1:1 ratio. The sequence was concealed until interventions were assigned. Randomisation was performed per each consecutive participant after verification of the exclusion criteria.
Allocation concealment (selection bias)	Low risk	Quote: "To ensure allocation concealment, treatment was assigned by telephone contact from the coordinating centre"
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Trial was open-label
Blinding of outcome assessment (detection bias) All outcomes except mortality	Low risk	Quote: "All outcome assessments were done under code by physicians blinded to the trial treatment."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The statistical analysis was based on the 'intention-to-treat' principle. None of the participants were lost to follow-up. However, SF measurements were only complete for all participants in the first year of the trial and decrease substantially thereafter to n = 32 in the combined group and n = 26 in the DFP group.
Selective reporting (reporting bias)	Low risk	All outcomes reported

Maggio 2009 *(Continued)*

Other bias	Unclear risk	"Only 21 (35%) subjects in the DFP-alone and 12 (24%) in the sequential DFP–DFO group withdrew definitely from the trial (Table V). The mean time for definitive withdrawal was 152 ± 103 (days) in DFP-alone versus 112 ± 76 (days) in the sequential DFP–DFO group respectively." "The planned duration of treatment was 5 years. However, because of the beneficial effects, in terms of serum ferritin levels reduction in the sequential DFP–DFO group, observed after the interim analysis performed at January 31, 2008 the trial was stopped before the planned 5 years of treatment were completed for all patients. Therefore, the mean duration of treatment was 2.5 ± 2.2 and 2.9 ± 2.1 years for DFP and sequential DFP–DFO group respectively" Judgement comment: withdrawal rate is high and the trial stopped early

Maggio 2020

Study characteristics	
Methods	**Study design**: multicentre RCT **Study grouping**: parallel-group **Study duration**: 12 months
Participants	**Baseline characteristics** **Pretreatment**: children in the deferiprone group were slightly younger when they received their first transfusion and first chelation **Overall** • Total # of participants: 390 • Age, mean (SD): 112.6 (56.16) months (n = 390) • Baseline ferritin levels (ng/mL) (mean (SD)): 2762.9 (2200.6), median 2016.9 (n = 384) • LIC (mg/g), mean (SD): 15.1 (13.0), median 10.6 (n = 177) **DFP** • Total # of participants: 193 • Age, N (%): < 6 years n = 59 (31%); 6 years up to 10 years n = 47 (24%); 10 years and over n = 87 (45%) • Sex, N (%): 80 (42%) female, 113 (58%) male • Sickle cell genotype, N (%): 12 participants (6%) with SCD • Thalassaemia genotype, N (%): 175 participants (91%) with β-thalassaemia major; 3 participants (2%) with thalassodrepanocytosis • Previous iron chelation, N (%): 166 (86%) • Duration of any iron chelation: NR • LIC (mg/g): NR • Splenectomy (%): NR • Quality of life: NR • Hb (g/l), mean (SD): NR **DFX** • Total # of participants: 197 • Age, N (%): < 6 years n = 58 (29%); 6 years up to 10 years n = 47 (24%); 10 years and over n = 92 (47%) • Sex, N (%): 93 (47%) female, 104 (53%) male • Sickle cell genotype N (%): 15 participants (8%) with SCD

Maggio 2020 *(Continued)*

- Thalassaemia genotype N (%): 177 participants (90%) with β-thalassaemia major; 2 participants (1%) with thalassodrepanocytosis
- Previous iron chelation, N (%): 170 (86%)
- Duration of any iron chelation: NR
- LIC (mg/g): NR
- Splenectomy (%): NR
- Quality of life: NR
- Hb (g/l), mean (SD): NR

Inclusion criteria

- Both genders aged from 1 month up to less than 18 years at the time of enrolment
- Any hereditary haemoglobinopathy requiring chronic transfusion therapy and chelation, including but not limited to thalassaemia syndromes and SCD
- Currently treated with DFO or DFX or DFP in a chronic transfusion programme receiving at least 150 mL/kg/year of packed RBCs (corresponding approximately to 12 transfusions), and naive to chelation treatment who have received at least 150 mL/kg of packed RBCs (corresponding to approximately 12 transfusions) in a chronic transfusion programme and with SF levels ≥ 800 ng/mL at screening
- Until availability of results from the PK Study (Study DEEP-1, EudraCT n. 2012-000658-67) for patients aged from 1 month to less than 6 years: known intolerance or contraindication to DFO
- Written informed consent obtained from legal guardian in accordance with the national legislations. Participant's informed assent will be collected according to his/her maturity and understanding.

Exclusion criteria

- Known intolerance or contraindication to either DFP or DFX
- Receiving DFX at a dose > 40 mg/kg per day or DFP at a dose > 100 mg/kg per day at screening
- Platelet count < 100,000 cells/µL at the washout visit (day –7)
- ANC < 1500 cells/µL at the washout visit
- Hb concentrations < 80 g/L at the washout visit
- Evidence of ALT concentrations > 5 times the ULN
- Iron overload from causes other than transfusional haemosiderosis
- Heart failure or severe arrhythmia or cardiac T2-star (T2*) < 10 ms
- Creatinine concentrations greater than the ULN for their age at the washout visit
- History of a clinically significant medical or psychiatric disorder
- Had received another investigational drug within 30 days before consent to study participation
- Had fever or other signs or symptoms of infection at the washout visit
- Concomitant use of trivalent cation-dependent medicinal products
- Positive test for beta-HCG (choriogonadotropin subunit beta)
- Lactating females

Interventions	**DFP intervention** DFP (ApoPharma; Toronto, ON, Canada) administered orally, daily at 75 to 100 mg/kg per day. DFP was formulated as an 80 mg/mL oral solution packaged in 250 mL bottles, using an administration device to ensure accurate measurement of dose volumes. If SF concentration increased by more than 20% compared with the previous test, or remained higher than 1500 ng/mL (no increase or any increase < 20%) in the absence of a downward trend over 3 months, DFP could be scaled up in steps of 12.5 mg/kg per day (to a maximum daily dose of 100 mg/kg). **DFX intervention** DFX (Novartis; Basel, Switzerland) administered as dispersible tablets at 125 mg, 250 mg and 500 mg. DFX daily dose ranged from 20 to 40 mg/kg per day as recommended in the summary of product characteristics. If SF concentration increased by more than 20% compared with the previous test, or remained higher than 1500 ng/mL (no increase or any increase < 20%) in the absence of a downward trend over 3 months, DFX could be increased in steps of 5 to 10 mg/kg per day (to a maximum daily dose of 40 mg/kg).

Maggio 2020 *(Continued)*

Outcomes	Adherence to iron chelation therapy rates reported as percentage compliance (and SD) only
Identification	**Sponsorship source**: EU FP7 under grant agreement no 261483 (Deferiprone Evaluation in Pediatrics, DEEP) **Country**: Albania, Cyprus, Egypt, Italy, Greece, Tunisia, UK **Setting**: outpatient **Comments**: EudraCT, 2012-000353-31 and ClinicalTrials.gov, NCT01825512 **Authors name**: Prof Aurelio Maggio **Institution**: Department of Hematology and Rare Diseases, V Cervello, Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italy **Email**: aurelio.maggio@villasofia.it **Address**: UOC Ematologia II con Talassemia, AO V Cervello, Palermo 90146, Italy
Notes	DEEP-2 study NCT01825512

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: "The randomisation sequence was generated directly into the electronic-case report form with blocks of variable size (4-6-8) and random seeds to ensure that allocation concealment could not be violated by guessing the allocation sequence at the end of each block."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was centralised and balanced by country. The randomisation sequence was generated directly into the electronic-case report form with blocks of variable size (4-6-8) and random seeds to ensure that allocation concealment could not be violated by guessing the allocation sequence at the end of each block."
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Comment: "This trial was open-label because of the different pharmaceutical forms and posology of the investigational medicinal products, which would have heavily affected the study feasibility had masking been attempted."
Blinding of outcome assessment (detection bias) All outcomes except mortality	High risk	Comment: "This trial was open-label because of the different pharmaceutical forms and posology of the investigational medicinal products, which would have heavily affected the study feasibility had masking been attempted." "No information on blinding of assessors although MRI scans and analysis of blood results performed centrally".
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there was imbalance between the number who withdrew between the 2 treatment arms. Twice as many withdrew from the trial in the DFP arm compared to the DFX arm. The authors reported per-protocol and modified ITT. They used last observation carried forward to account for missing data.
Selective reporting (reporting bias)	Low risk	Comment: outcomes there were planned to be reported have been reported in the manuscript or planned to be reported elsewhere.

Maggio 2020 *(Continued)*

Other bias	Low risk	Comment: no other obvious sources of bias.

Mourad 2003

Study characteristics	
Methods	2-arm parallel RCT Number of centres: 1 Trial dates: not stated Duration of treatment: 1 year Follow-up: none Trial undertaken: Chronic Care Centre, Beirut, Lebanon
Participants	Number randomised: 25 (treatment group: 14; comparator group: 11) Number analysed: 25 (treatment group: 14; comparator group: 11) β-thalassaemia participants, severely iron overloaded and previously poorly chelated Age range: 12 to 40 years Sex: treatment: 43% male, comparator: 64% male Ethnicity: not stated
Interventions	**DFO** • DFO by subcutaneous injection, 40 to 50 mg/kg 8 to 12 hours a day, 5 to 7 days/week **DFP/DFO** • DFP 75 mg/kg/day orally in 3 divided doses, 7 days a week, DFO by subcutaneous injection, daily dose of 2 g over 8 to 12 hours, 2 days a week
Outcomes	**Adherence** see compliance below **Trial-reported outcomes** 1. Mean serum iron concentration at baseline, 6 and 12 months (primary outcome) 2. Number RBC units during the trial 3. Iron excretion at 1 and 12 months 4. Hb level measured weekly for 3 months then monthly for 9 months 5. Liver function measured weekly for 3 months then monthly for 9 months 6. Renal function measured weekly for 3 months then monthly for 9 months 7. Side effects 8. Participant compliance: compliance was assessed by the number of vials of DFX or tablets of DFP used. Safety was determined by detailed clinical and laboratory examination. Participants were also asked to complete questionnaires about any side effects they experienced.
Identification	Source of funding: not stated
Notes	Prior exposure to iron chelators: DFO, fewer than 4 times a week, dose and duration not reported Sample size calculation not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The authors did not report any information about how randomisation was undertaken

Mourad 2003 *(Continued)*

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

Olivieri 1997

Study characteristics	
Methods	2-arm parallel RCT Number of centres: 2 Trial dates: November 1993 to September 1995 Duration of treatment: analysis undertaken after 24 months (mean (SD) duration 33 (1.0) months, range 24 to 43 months) Follow-up: none Trial undertaken: Hospital Centres in Toronto and Montreal, Canada. These data are from the Toronto participants only.
Participants	**Baseline characteristics** Number randomised: 64 (DFO: 32; DFP: 32) Number analysed: 37 (DFO: 18; DFP: 19). The trial reports details for why 6 and 7 participants respectively were not included in the analysis. The remaining participants had not completed 24 months treatment at the time of analysis for this trial report. **DFP (L1)** • Age: not reported • Sex: F: 11; M: 14 • Thalassaemia genotype (%): thalassaemia major: 100% • Baseline ferritin levels (ng/mL) mean (SD): 2194 (1251) • Previous iron chelation: not reported • Duration of any iron chelation (duration of treatment in this trial - mean (SD) months): 11.0 (4.2) range 2 to 15 • LIC (mg/g): 9.56 (4.77), range 2.7 to 21.7

Olivieri 1997 *(Continued)*

- Splenectomy n (%): not reported
- QoL mean (SD): not reported
- Hb, g/L: not reported

DFO

- Age: not reported
- Sex: F: 11 M: 14
- Thalassaemia genotype (%): thalassaemia major: 100%
- Baseline ferritin levels (ng/mL) mean (SD): 2089 (048)
- Previous iron chelation: not reported
- Duration of any iron chelation (duration of treatment in this trial - mean (SD) months): 11.63 (3.26), range 2 to 15 months
- LIC (mg/g): 7.43 (3.59), range 2.4 to 15.7
- Splenectomy n (%): not reported
- QoL mean (SD): not reported
- Hb, g/L: not reported

Inclusion criteria: diagnosed with homozygous β-thalassaemia, 10 years of age or older, willing to participate in the trial

Exclusion criteria:

- Refusal to participate in the screening
- Previously treated with DFP
- Serious adverse reactions to DFO
- Failed to attend 20% of the visits in the first 3 months of the trial
- Receiving other investigational drugs
- Past history of malignancy
- Medical, psychological or psychiatric risk
- Therapy with an investigational drug would be unwise
- Pregnant or breastfeeding
- Not using a reliable birth control method

Pre-treatment:

- Stratified into high (7 mg Fe/g dry weight liver tissue) and low iron-overloaded (7 mg Fe/g dw) according to their hepatic iron concentration as assessed either by liver biopsy or a SQUID (or both)
- 8 participants have been withdrawn from the study due to AEs (2), family reasons (1), psychiatric disorder (1), chronic neutropenia prior to starting on DFP (2), bone marrow transplantation (1) and non-compliance with the trial protocol (1)
- 25 participants on DFP and 26 participants on DFO have been used in the present analysis
- Author goes on to report that results of n = 5 in DFO were not evaluated as there was no compliance data. A further n = 5 participants on DFP and n = 2 were excluded for the analysis of the correlation between compliance + successful outcome (as measured by LIC) as there were 6 months of data available. Therefore, for the main outcome the actual N = 39 (n = 20 in DFP and n = 19 in DFO.

Interventions	**DFP (L1)** • DFP 75 mg/kg/day in 3 divided doses **DFO** • DFO 50 mg/kg/night, 4 to 7 night/week
Outcomes	**Adherence** see adherence below **Trial-reported outcomes**

Olivieri 1997 *(Continued)*

	1. Change in LIC (measured by SQUID or biopsy) between 12 months prior to randomisation and 24 months duration on trial treatment 2. Adherence to iron chelation therapy rates defined as per cent of doses administered (number of doses of the iron chelator taken, out of number prescribed), measured for a minimum of 3 months
Identification	**Sponsorship source**: no sponsorship stated **Country**: Canada **Setting**: Transfusion Clinic **Authors name**: Nancy Olivieri **Institution**: University of Toronto **Source of funding**: not stated
Notes	Prior exposure to iron chelators: not reported Abstract publication. Some data from Pope 1995 thesis included for baseline characteristics. Sample size calculation not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "After stratification patients by LIC (>7mg Fe/g; < 7mg Fe/g) 'patients were assigned by a research pharmacist who did not know the patients"
Allocation concealment (selection bias)	Unclear risk	The authors did not report any information about how treatment allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	1 treatment a pump and 1 treatment a tablet; participants and researchers would not be blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes except mortality	Unclear risk	The authors did not report any information as to whether outcome assessors were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	The trial analysed data from 58% of randomised participants. Of the 42% randomised participants who were not available for outcome analysis: • 22% randomised participants had not completed the required 24 months treatment at the time of analysis for the trial report • 16% DFP-treated participants and 5% DFO-treated participants were withdrawn due to treatment-induced side effects This missing data may inappropriately affect the statistical findings of the trial
Selective reporting (reporting bias)	Low risk	All outcomes pre-specified were reported in the manuscript
Other bias	Unclear risk	The trial was reported in an abstract, thus there are few data available to make an assessment of whether the trial was free of other bias. Trial stopped early by manufacturer

Pennell 2006

Study characteristics	
Methods	2-arm parallel RCT Number of centres: 4 Trial dates: December 2002 to March 2005 Duration of treatment: 1 year Follow-up: outcome data recorded for duration of treatment Trial undertaken: 4 participating centres in Italy and Greece
Participants	Number randomised: 61 DFO: 32; DFP: 29 Number analysed: variable across outcomes. Minimum and maximum numbers analysed were: treatment group: 30 to 32; comparator group: 27 to 29. Trial reported details as to why data from 1 participant in the treatment group and 2 in the comparator group were withdrawn from treatment. Transfusion-dependent homozygous participants with β-thalassaemia major Age: mean (SD) treatment group: 26.2 (4.7) years; mean (SD) comparator group: 25.1 (5.8) years Sex: treatment group: 50% male; comparator group: 52% male Ethnicity: Greek/Italian: treatment group: 18/14; comparator group: 16/13
Interventions	**DFO** • DFO by subcutaneous injection, 50 mg/kg for 5 or more days a week **DFP** • DFP initial dose 75 mg/kg/day increasing to 100 mg/kg/day. Mean actual dose: 92 mg/kg/day.
Outcomes	**Adherence rates**: DFP compliance was measured using the Medication Event Monitoring System device (Aardex, Zug, Switzerland) and calculated as the percent of openings with an interval longer than 4 hours recorded, divided by number of doses prescribed. DFO compliance was calculated as the percentage of completed infusions, as determined by the Crono pumps, divided by the number of infusions prescribed. **Trial-reported outcomes** 1. Change over 1 year in myocardial T2* (primary outcome) 2. Cardiac volumes and function 3. LIC 4. SF 5. ANC 6. AEs 7. ALT 8. Serum zinc levels 9. Serum creatinine levels
Identification	Trial sponsor: Apotex (manufacturer of DFP)
Notes	Prior exposure to iron chelators: DFO at a mean (SD) dose of 39 (8) mg/kg/day for 5 to 7 days/week Sample size calculation reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors did not report any information about how randomisation was undertaken

Pennell 2006 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	The authors did not report any information about whether treatment allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Open-label; one treatment subcutaneous and the other oral so not possible to mask treatments
Blinding of outcome assessment (detection bias) All outcomes except mortality	Low risk	The primary outcome was independently measured in a different country (UK) to where the trial took place and the findings were not communicated back to the clinicians during the course of the trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the analysis of the outcomes SF and AEs Data from 1 participant in the treatment (DFO) group were not included in the analysis of the cardiac outcomes (primary outcome) and last observation carried forward method was used to accommodate the missing data from 3 other participants (1 treatment group and 2 from the comparator group) in the cardiac outcomes (primary outcome) 2 participants in each treatment group did not have a LIC assessment at 12 months and the data from these participants were missing from the analysis
Selective reporting (reporting bias)	High risk	The following pre-specified outcomes were not reported in the manuscript: ANC, ALT, serum zinc levels and serum creatinine levels
Other bias	High risk	There are several imbalances in baseline characteristics between the 2 interventions including a major imbalance in SF measures with the DFO group having much higher levels as well as a greater proportion of participants with severe iron overload (above 2500 µg/L)

Pennell 2014

Study characteristics	
Methods	**Study design**: RCT **Study grouping**: parallel-group CORDELIA was a prospective, multinational, randomised, open-label, parallel-group, phase 2 trial. A total of 81.2% of participants (n = 160) completed 1 year of treatment
Participants	"Overall, 925 patients were screened and 197 randomized. The majority of patients screened were β-thalassemia major patients (902/925; 99.1%). Other patients who were screened and for whom underlying anaemia was captured had low/intermediate 1 myelodysplastic syndrome (n = 4), Diamond–Blackfan anaemia, β-thalassemia intermedia, congenital dyserythropoietic anaemia, and paroxysmal nocturnal haemoglobinuria (all n = 1). Only β-thalassemia major patients fulfilled the inclusion criteria and were enrolled in the study. A total of 81.2% of patients (n = 160) completed 1 year of treatment". **Baseline characteristics** **DFX (Exjade)** • Total # of participants: 98 • Age mean (SD): 19.9 (6.5)

Pennell 2014 *(Continued)*

- Sex (M:F ratio n): 58:40
- Thalassaemia genotype (%): thalassaemia major: 100%
- Previous iron chelation: DFO: 41 (42.7); DFP: 9 (9.4); DFO + DFP: 21 (21.9); DFX: 18.1 (8.8); unknown or irregular: 7 (7.3)
- Duration of any iron chelation mean (SD) years: 14.0 (7.0)
- LIC (mg Fe/g dw): < 7: 11 (12.1); 7 to < 15: 14 (15.4); ≥ 15: 66 (72.5)
- Splenectomy n (%): not reported
- QoL (mean (SD)): not reported
- Median SF (range), ng/mL (per protocol population): 5062 (613 to 15331)

DFO (Desferal)

- Total # of participants: 99
- Age mean (SD): 19.7 (6.3)
- Sex (M:F ratio n): 57:42
- Thalassaemia genotype (%): thalassaemia major: 100%
- Previous iron chelation: DFO: 39 (42.9); DFP: 5 (5.5); DFO + DFP: 21 9 (23.1); DFX: 23 (25.3); unknown or irregular: 3 (3.3)
- Duration of any iron chelation mean (SD) years: 14.3 (7.2)
- LIC (mg Fe/g dw): 7: 8 (9.9); 7 to 15: 14 (17.3); ≥ 15: 59 (72.8)
- Splenectomy n (%): not reported
- QoL (mean (SD)): not reported
- Median SF (range), ng/mL (per protocol population): 4684 (677 to 13,342)

Inclusion criteria: people with β-thalassaemia major, Diamond–Blackfan anaemia, low/intermediate myelodysplastic syndromes, or sideroblastic anaemia, aged ≥ 10 years with myocardial T2* 6 to 20 ms, LVEF ≥ 56%, R2 MRI LIC ≥ 3 mg Fe/g dw, lifetime history of ≥ 50 units RBC transfusions, and receiving ≥ 10 units/year of RBC transfusions

Exclusion criteria: participants with serum creatinine above the ULN or significant proteinuria (urinary protein/creatinine ratio ≥ 1.0 mg/mg in a non–first-void urine sample at baseline; people with ALT 5 x the ULN only if their LIC was 10 mg Fe/g dw; considerable impaired GI function or GI disease; history of clinically relevant ocular and/or auditory toxicity related to iron chelation; therapy, and history of HIV seropositivity or malignancy within the past 5 years; clinical symptoms of cardiac dysfunction (shortness of breath at rest or exertion, orthopnoea, exercise intolerance, lower-extremity edoema, arrhythmias)

Interventions	**DFX (Exjade)** • Once-daily DFX starting dose was 20 mg/kg per day for 2 weeks, followed by 30 mg/kg per day for 1 week, and then continued with 40 mg/kg per day **DFO (Desferal)** • An intensified dosing regimen of DFO was administered at 50 to 60 mg/kg per day via subcutaneous infusion over 8 to 12 hours, 5 to 7 days a week, in accordance with Thalassaemia International Federation Guidelines Mean actual dose over 1-year treatment was 36.7 6 4.2 mg/kg per day DFX (range, 19.7 to 43.3 mg/kg per day). Mean actual dose of DFO was 41.5 6 8.7 (13.2 to 60.2) mg/kg per day, when normalised to a 7-day regimen
Outcomes	**Adherence** to iron chelation therapy rates: not stated how adherence was measured **Trial-reported outcomes** 1. Ratio of Gmean myocardial T2* after 1 year of treatment with DFX divided by the ratio of Gmean for DFO 2. Change in LVEF after 1 year of treatment, assessed by absolute change from baseline CMR 3. Absolute change from baseline in LIC after 1-year treatment

Pennell 2014 *(Continued)*

	4. Absolute change from baseline in SF after 1-year treatment
Identification	**Sponsorship source**: Novartis Pharma AG **Country**: multinational, 11 countries **Setting**: 22 centres across 11 countries **Comments**: the authors thank Debbi Gorman of Mudskipper Business Ltd for medical editorial assistance. Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals. **Authors name**: Dudley J. Pennell **Institution**: National Institute for Health, Research Cardiovascular Biomedical Research Unit **Email**: d.pennell@ic.ac.uk **Address**: National Institute for Health Research Cardiovascular Biomedical Research Unit, Royal Brompton Hospital, Sydney Street, London, SW3 6NP, UK
Notes	Novartis Pharmaceuticals Corporation (East Hanover, NJ, USA) co-ordinated the design and execution of this trial and contributed to the analysis and interpretation of the trial data. Novartis Pharmaceuticals Corporation also collaborated with the external authors to assist in the development and approval of the manuscript for publication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "22 centers across 11 countries. Following a 35-day screening phase, patients were randomized in a 1:1 ratio". Randomisation was based on permuted blocks; stratification by centre was not conducted.
Allocation concealment (selection bias)	Unclear risk	Judgement comment: no description of allocation concealment except that randomisation was based on permuted blocks
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Judgement comment: open-label trial - subcutaneous pump versus oral tablet - difficult to blind
Blinding of outcome assessment (detection bias) All outcomes except mortality	Low risk	Quote: "Core laboratories were blinded to treatment allocation.In order to eliminate potential unrecognized biases, the core clinical trial team was blinded to the treatment assignment prior to the database lock for the primary analysis."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Judgement comment: 21 withdrawn DFO arm, 16 in DFX (78 to 82 completed trial). Efficacy outcomes reported per protocol and safety in the participants who received the trial drug.
Selective reporting (reporting bias)	Unclear risk	Investigator-reported AEs, regardless of causality, were reported in 65 (67.7%) DFX participants and 69 (75.8%) DFO participants (supplemental Table 2). AEs suspected to be related to trial drug occurred in 35.4% of DFX participants and 30.8% of DFO participants. Judgement comments: it is unclear if investigator-reported AEs and those suspected to be related to trial drug include the same AEs. Also, they only report the end of trial LIC value for the DFX group.

Pennell 2014 *(Continued)*

Other bias	Low risk	The trial appears to be free of other sources of bias

Taher 2017

Study characteristics	
Methods	**Study design**: multicentre RCT conducted in several countries **Study grouping**: parallel-group **Study duration**: 24 weeks
Participants	**Baseline characteristics** **DFX film-coated tablet** • Total # of participants: N = 87 • Age: 34.6 (19.97) • Sex: F: 41 • Thalassaemia genotype N (%): thalassaemia major: 70 (80.5) • Previous iron chelation: 79 (90.8) • Median SF (range), ng/mL: 2983 (939 to 8250) • Splenectomy n (%): not reported • QoL mean (SD): not reported • Hb, g/L: not reported **DFX dispersible tablet** • Total # of participants: N = 86 • Age: 35.1 (18.60) • Sex: F: 47 • Thalassaemia genotype N (%): thalassaemia major: 70 (81.4) • Baseline ferritin levels (ng/mL) mean (SD): 2089 (048) • Previous iron chelation: 77 (89.5) • Median SF (range), ng/mL: 2485 (915 to 8250) • Splenectomy n (%): not reported • QoL mean (SD): not reported • Hb, g/L: not reported **Inclusion criteria**: • Males and females aged ≥ 10 years • Transfusion-dependent thalassaemia and iron overload, requiring DFX dispersible tablet at doses of ≥ 30 mg/kg/day as per the investigator's decision or participants with very low, low or intermediate (int) risk myelodysplastic syndrome and iron overload, requiring DFX dispersible tablet at doses of ≥ 20 mg/kg/day as per the investigator's decision • History of transfusion of at least 20 PRBC units and anticipated to be transfused with at least 8 units of PRBCs annually during the study • SF > 1000 ng/mL, measured at screening Visit 1 and screening Visit 2 (the mean value will be used for eligibility criteria) **Exclusion criteria**: • Creatinine clearance below the contraindication limit in the locally approved prescribing information. Creatinine clearance will be estimated from serum creatinine at screening Visit 1 and screening Visit 2 and the mean value will be used for eligibility criteria

Taher 2017 *(Continued)*

	• Serum creatinine > 1.5 x ULN at screening measured at screening Visit 1 and screening Visit 2 (the mean value will be used for eligibility criteria) • ALT (SGPT) > 5 x ULN, unless LIC confirmed as > 10 mg Fe/dw within 6 months prior to screening Visit 1. Significant proteinuria as indicated by a urinary protein/creatinine ratio > 0.5 mg/mg in a non-first void urine sample at screening Visit 1 or screening Visit 2 • Participants with significant impaired GI function or GI disease that may significantly alter the absorption of oral DFX (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhoea, malabsorption syndrome or small bowel resection) • Liver disease with severity of Child-Pugh Class B or C
Interventions	**DFX film-coated tablets** • DFX film-coated provided as 90 mg, 180 mg and 360 mg film-coated tablets for oral use **DFX dispersible tablet** • DFX dispersible tablet provided as 125 mg, 250 mg and 500 mg dispersible tablets for oral use
Outcomes	**Adherence to iron chelation therapy rates** Compliance with medication as assessed by relative consumed tablet count **Trial-reported outcomes** 1. Overall safety of both DFX formulations, measured by frequency and severity of AEs and changes in laboratory values from baseline to 24 weeks 2. Evaluation of both formulations on selected GI AEs (diarrhoea, constipation, nausea, vomiting and abdominal pain) during treatment 3. Estimation of treatment compliance 4. Evaluation of both formulations on participant satisfaction, palatability and GI symptoms using PROs 5. Evaluation of the pharmacokinetics of both formulations 6. Reported % compliant with upper and lower percentages
Identification	**Sponsorship source**: Novartis Pharmaceuticals **Country**: USA **Comments**: NCT02125877 **Authors name**: Ali Taher **Institution**: American University of Beirut Medical Center **Email**: ataher@aub.edu.lb **Address**: Haematology and Oncology, Department of Internal Medicine, Faculty of Medicine, American University of Beirut Medical Center, Beirut, Lebanon
Notes	Sample size calculation not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was stratified by underlying disease and previous chelation treatment." No clear description of randomisation or if participants were randomised centrally

Taher 2017 *(Continued)*

Allocation concealment (selection bias)	High risk	Quote: "Post- hoc analyses identified that 23 patients on FCT (26%) were started on a dose that was higher than recommended in the protocol compared with 8 patients (9.3%) on DT (not recognized or reported by the investigators as dosing error)." Judgement comment: the trial was open-label and most participants had been on 1 or the other of the trial drugs prior to the trial - doses may have corresponded to prior dosing since there was no description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Judgement comment: open-label
Blinding of outcome assessment (detection bias) All outcomes except mortality	High risk	No description of how outcome assessment was performed - centrally or blinded open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Overall, all patients were satisfied with their medicine during the study period; satisfaction scores were higher with deferasirox FCT compared with DT at all visits." Judgement comment: no data provided on number of participants or scores, just general statements
Selective reporting (reporting bias)	High risk	Quote: "patients discontinued treatment because of AEs (n = 10), protocol deviation (n = 5), withdrawal of consent (n = 3), patient guardian decision (n = 2), and other reasons (administrative problems, death, and physician's decision, n = 1 each)." Judgement comment: investigators do not report all outcomes by treatment assignment, and AEs and SAEs are reported as suspected relationship to trial drug and occurring in > or equal to 10%
Other bias	Unclear risk	"The absolute reduction in median serum ferritin (range) in patients receiving FCT was –350 (–4440–3572) ng/mL and in those receiving DT was –85.5 (–2146–8250) ng/mL); these correspond to a relative change of –14.0% with FCT and –4.1% with DT." Judgement comment: some of the difference in change could be accounted for by more participants starting on a higher dose of film-coated tablet

Tanner 2007

Study characteristics	
Methods	2-arm parallel RCT Number of centres: multicentre (12 centres) Duration of treatment: 12 months Follow-up: not stated Trial undertaken: thalassaemia outpatient clinics in Sardinia
Participants	Number randomised: 65 (treatment group: 33; comparator group: 32)

Tanner 2007 *(Continued)*

	Number analysed: not reported Number completing treatment: 60 (treatment group: 32; comparator group: 28). The reason for the withdrawal was not fully reported by the trial authors Participants aged 18 years or older with a diagnosis of β-thalassaemia, currently maintained on subcutaneous DFO and with a myocardial T2* between 8 and 20 ms Age: treatment group: mean (SD) 28.7 (5.3) years; comparator group: mean (SD) 28.8 (4.2) years; age range for both arms was 18 to 42 years Sex: treatment group: 39% male; comparator group: 44% male Ethnicity: not stated
Interventions	**DFO** • DFO 40 to 50 mg/kg subcutaneously for 5 days a week (DFO actual dose: 43.4 mg/kg for 5 days) with an oral placebo (no further details reported) **DFO/DFP** • DFO 40 to 50 mg/kg subcutaneously for 5 days a week (DFO actual dose: 34.9 mg/kg for 5 days) with DFP 75 mg/kg daily for 7 days a week
Outcomes	**Adherence** see compliance below **Trial-reported outcomes** 1. Change over 1 year in myocardial T2* (primary outcome) 2. Change in liver T2* at 12 months 3. SF 4. Left ventricular volume and function 5. Brachial artery reactivity as a marker of heart failure 6. Participant compliance with chelation treatments: DFO compliance was calculated as the percentage of completed infusions, as determined by the Crono pumps, divided by the number of infusions prescribed. DFP/placebo compliance was measured through pill counting at the bi-monthly visits 7. AEs 8. BNP test
Identification	Source of funding: CORDA, Royal Brompton & Harefield Hospitals Charitable funds, Cooley's Anemia Foundation, Apotex, UK Thalassaemia Society, University College London Special Trustees Charity
Notes	Prior exposure to iron chelation: DFO mean (SD) dose 36.4 (11.1) mg/kg per day for 5.5 day/week (equivalent to 40.5 mg/kg for 5 day/week). Participants were excluded if they had previously received DFP. Sample size calculation reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors did not report any information about how randomisation was undertaken
Allocation concealment (selection bias)	High risk	Trial reports that the participants and clinicians were aware of how treatment was to be allocated
Blinding of participants and personnel (performance bias)	Unclear risk	The authors did not report any information as to whether participants or personnel were blinded to treatment allocation

Tanner 2007 *(Continued)*

All outcomes except mortality or other objective outcomes		
Blinding of outcome assessment (detection bias) All outcomes except mortality	Unclear risk	The authors did not report any information as to whether outcome assessors were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	As the trial does not report the number of participants included in each outcome assessment. The trial reports the number completing treatment and the reasons why 3 participants in the treatment group (1 adverse event and 2 participant requests) and 4 participants in the comparator group (3 adverse events and 1 participant request) were withdrawn from the trial.
Selective reporting (reporting bias)	Low risk	All outcomes pre-specified were reported in the manuscript
Other bias	Low risk	The trial appears to be free of other sources of bias

Vichinsky 2007

Study characteristics	
Methods	**Study design**: RCT **Study grouping**: parallel-group The study duration was 52 weeks Participants were recruited by investigators at 44 sites in the USA, France, Italy, UK and Canada
Participants	**Baseline characteristics** **DFX** • Total # of participants: 132 • Age: 15 range 3 to 54 • Sex (female %): 60.6 • Sickle cell genotype N (%): 100 • Baseline ferritin levels (ng/mL) median (min to max): 3460 (1082 to 1201) • Previous iron chelation %: 62.9 • Splenectomy n (%): not reported • QoL mean (SD): not reported **DFO** • Total # of participants: 63 • Age: 16, range 3 to 51 • Sex (female %): 55.6 • Sickle cell genotype N (%): 100 • Baseline ferritin levels (ng/mL) median (min to max): 2834 (1015 to 15,578) • Previous iron chelation %: 60.3 • Splenectomy n (%): not reported • QoL (mean (SD)): not reported **Age group (% DFX, DFO)**

Vichinsky 2007 *(Continued)*

< 6 years: 3.0, 4.8
6 to < 12 years: 22.7, 23.8
12 to < 16 years: 25.0, 20.6
16 to < 50 years: 47.7, 49.2
50 to < 65 years: 1.5, 1.6

Inclusion criteria:

- People with SCD ≥ to 2 years of age and with iron overload from repeated blood transfusions
- People receiving regular blood transfusions or those sporadically transfused who received at least 20 units of packed RBCs or equivalent were eligible
- Prior chelation therapy was permitted but was not mandatory
- The serum ferritin level for entry into the screening period of this study was ≥ 1000 µg/L

Exclusion criteria

- People were excluded if they had a serum creatinine above the ULN
- Significant proteinuria (as indicated by a urinary protein:creatinine ratio of ≥ 0.5 confirmed at 2 visits)
- Active hepatitis B or C
- Second and third atrioventricular block, QT interval prolongation, or therapy with digoxin or similar medications
- Treatment with beta-blockers or angiotensin-converting enzyme inhibitors was permitted. Those with chelation therapy-associated ocular toxicity were excluded.

Interventions

DFX

- The initial 24 participants enrolled were randomised to receive DFX 10 mg/kg, all subsequent participants randomised to DFX were dosed at 10 to 30 mg/kg according to baseline LIC. DFX was given once daily each morning as a dispersed solution in water, half-an-hour before breakfast. The dose of DFX was reduced by 1 dose level and not re-escalated for participants 15 years and older if serum creatinine increased 33% above baseline on 2 consecutive occasions. For children less than 15 years of age, the dose was only decreased if these values were also above the age-appropriate ULN. DFX was interrupted for moderate or severe skin rash and re-instituted at half the initial dose, and dose re-escalation was permitted.

DFO

- DFO was administered as a slow subcutaneous infusion over 8 to 12 hours using electronic Microject Chrono infusion pumps on 5 to 7 days a week. In order to facilitate the comparison of different schedules, all DFO doses reported were normalised to administration for 5 days/week (i.e. 50 mg/kg administered 7 days/week would be reported as 70 mg/kg)

Outcomes

Adherence to iron chelation therapy rates

Compliance. For DFX, compliance was assessed by counting the number of tablets returned in bottles at each visit. For DFO, the numbers of vials returned at each visit were counted

Trial-reported outcomes

1. Safety assessments
2. Laboratory assessments were performed at least monthly and included complete blood counts with differential counts. Biochemistry testing included electrolytes, glucose, liver function tests, gamma-glutaryl-transferase, lactate dehydrogenase, cholesterol, triglycerides, uric acid, total protein, C-reactive protein, copper and zinc levels. Iron parameters included total iron, transferrin, transferrin saturation and ferritin. Urinary testing performed on random collections included determination of creatinine, total protein and albumin
3. Physical examinations, ECGs, audiometry and ophthalmological tests were performed at baseline, 12, 24, 36 and 52 weeks. In participants less than 16 years of age, additional assessments included growth velocity and pubertal stage
4. Efficacy assessments. LIC was determined by SQUID biospectrometry at baseline, 24 and 52 weeks. The 24-week assessment was performed primarily for safety purposes, and the change in LIC was cal-

Vichinsky 2007 *(Continued)*

	culated between baseline and 52 weeks. SF was assessed monthly during the trial and the change was determined using the baseline and final ferritin level
Identification	**Sponsorship source**: Novartis Pharmaceuticals **Country**: international (Canada, France, Italy, UK and USA) **Setting**: medical centre outpatient **Authors name**: Elliott Vichinsky **Institution:** Children's Hospital and Research Center at Oakland **Email**: evichinsky@mail.cho.org **Address:** Children's Hospital and Research Center at Oakland, 747 52nd Street, Oakland, CA 94609, USA Novartis Pharmaceuticals Corporation (East Hanover, NJ, USA) co-ordinated the design and execution of this trial and contributed to the analysis and interpretation of the trial data. Novartis Pharmaceuticals Corporation also collaborated with the external authors to assist in the development and approval of the manuscript for publication
Notes	Sample size calculation reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation was performed using an interactive voice response system"
Allocation concealment (selection bias)	Unclear risk	Quote: "stratified according to the following age groups: 2 to < 6 years, 6 to < 12 years, 12 to < 16 years and 16 years and older. The randomisation sequence included permuted block groups of six patients for each of the three age strata." Judgement comment: some of the age groups had few participants and unclear if allocation would remain concealed with permuted block groups of 6 participants
Blinding of participants and personnel (performance bias) All outcomes except mortality or other objective outcomes	High risk	Judgement comment: no mention of blinding, but DFO is delivered by infusion pumps and DFX is a solution in water, so blinding not feasible
Blinding of outcome assessment (detection bias) All outcomes except mortality	High risk	Judgement comment: no description of blinding: Novartis Pharmaceuticals Corporation (East Hanover, NJ, USA) co-ordinated the design and execution of this trial and contributed to the analysis and interpretation of the trial data. The data were analysed under supervision of the trial statistician and were reviewed by the investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported. 8 participants did not complete and were not included. 6 in DFX arm withdraw consent, one in DFO arm. 3 DFO non-compliant, 2 DFX and 1 DFO lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Quote: "Adverse events, irrespective of the relationship to study medication, which occurred in more than 10% of patients receiving either treatment, are shown in Table III. As arbitrarily defined by an increased frequency of at least 5% indicating a potential relationship to drug administration."

Vichinsky 2007 *(Continued)*

		Judgement comment: do not report the total number of AEs in all participants, as well there was a substantial number of participants experience SAEs and there is no list of the type except for pain crisis: the number of participants receiving DFX and DFO that reported SAEs was similar (46.2% and 42.9% respectively) and the most common SAE in both groups was sickle cell anaemia with crisis (33.3% and 31.7% respectively). Also, the table of AEs reports % and no totals so impossible to determine the total number of participants with an AE.
Other bias	Unclear risk	Quote: "The reasons for withdrawal of consent were not included in the database." Quote: "The initial 24 patients enrolled were randomised to receive deferasirox 10 mg/kg or deferoxamine at recommended doses of 20–60 mg/kg based on initial LIC. Subsequently, additional safety information became available for deferasirox suggesting a need to modify the starting dose (Cappellini et al, 2006). Therefore, following the enrolment of the first 24 patients, the study was amended so that all subsequent patients randomised to deferasirox were dosed at 10–30 mg/kg according to baseline LIC". Judgement comment: it is important to understand the reasons for withdrawals and also the nature of the missing safety information, which may have implications for dosing and effects of the dosing amendment

ADRs: adverse drug reactions
AEs: adverse events
ALT: alanine aminotransferase
ANC: absolute neutrophil count
BNP: brain natriuretic peptide
CBC: complete blood count
CI: confidence interval
CMR: cardiovascular magnetic resonance imaging
DFO: deferoxamine
DFP: deferiprone
DFX: deferasirox
dw: dry weight
ECGs: electrocardiograms
FBC: full blood count
GI: gastrointestinal
Hb: haemoglobin
HRQoL: health-related quality of life
ICT: iron chelation therapies
IQR: interquartile range
ITT: intention-to-treat
LVEF: left ventricular ejection fraction
LIC: liver iron concentration
MRI: magnetic resonance imaging
N/A: not applicable
NR: not reported
PK: pharmacokinetic
PRBC: packed red blood cell
QoL: quality of life
RBCs: red blood cells
RCT: randomised controlled trial
SAEs: serious adverse events
SCr: sickle cell retinopathy
SD: standard deviation
SE: standard error
SF: serum ferritin
SGPT: serum glutamate-pyruvate transaminase
SQUID: Superconducting Quantum Interference Device

UIE: urinary iron excretion
ULN: upper limit of normal
WBC: white blood count

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

Study	Reason for exclusion
Abu 2015	Wrong study design - qualitative interview questionnaire used
Adibi 2012	Wrong intervention: silymarin as intervention of interest
Aftab 2017	Wrong study design
Al Kloub 2014	Wrong study design - qualitative interview questionnaire used
Al Kloub 2014a	Wrong study design - cross-sectional study
Allemang 2016	Wrong study design
Al-Momen 2020	Wrong intervention: green tea as intervention of interest
Al Refaie 1995	Wrong study design - medication study - not an RCT
Alvarez 2009	Wrong study design - medication study - not an RCT
Anderson 2017	Wrong study design
Anderson 2018	Wrong study design
Angelucci 2005	Wrong study design: subgroup analysis of a combination of two wider studies (non RCT)
Ansari 2017	Wrong study design: non RCT in medicinal trial
Arian 2018	Wrong study design
Armstrong 2011	No intervention
Aydinok 2016	Wrong intervention: vitamin C as intervention of interest
Aziz 2021	Wrong study design - no comparison group
Bala 2014	No intervention
Bartin Gooden 2015	Wrong study design
Bazpour 2019	Wrong study design
Belgrave 1989	No intervention
Bellanti 2017	Wrong study design: focused on dosage of single drug, not designed to measure adherence
Bellanti 2017a	Wrong study design: focused on assessing optimal sampling times, not designed to measure adherence
Berkovitch 1995	Not designed to measure adherence to iron chelation therapy

Study	Reason for exclusion
Biabani 2020	Wrong study design
Bin Ahmed 2018	Wrong study design - not designed to assess adherence
Canatan 2004	Wrong study design: non RCT in medicinal trial
Cappellini 2005b	Wrong study design: non RCT in medicinal trial
Cappellini 2017	Wrong study design: non RCT in medicinal trial
Chakrabarti 2013	Not designed to measure adherence to iron chelation therapy
Chaudhary 2021	Review - references checked
Cheesman 2018	Wrong study design
Daar 2010	Wrong study design - non-randomised, single-centre study
Darvishi-Khezri 2017	Wrong intervention: silymarin vs placebo
Deugnier 2005	Wrong study design: subgroup analysis of a combination of two wider studies (non RCT)
Deugnier 2010	Wrong study design: subgroup analysis of a combination of two wider studies (non RCT)
Ding 2017	Wrong study design
Elalfy 2016	Wrong study design
Elalfy 2018	Wrong study design
Emami Zeydi 2018	Review
Eshghi 2018	Wrong study design
EUCTR 2007-000766-20-IT	Wrong study design
EUCTR 2007-004008-10	Wrong study design - no comparator group
EUCTR 2015-003225-33-GR	Wrong intervention
Farhady 2020	Wrong study design
Galanello 2006b	Wrong study design - non RCT in medical intervention
Gallo 2014	Wrong study design
Gomber 2004	No intervention
Gordon 2018	Wrong study design
Habibian 2014	Wrong study design - not designed to measure adherence
Hagag 2013	Wrong intervention: silymarin is intervention of interest
Hamed 2020	Wrong intervention: deferasirox plus various adjunct therapies to improve efficacy

Study	Reason for exclusion
Hankins 2020	Review
Hankins 2021	Review/commentary
Inusa 2022	Wrong study design: non RCT extension of a previous trial
IRCT 2009 0813002342N9 (Rafati 2022)	Wrong study design: not designed to assess adherence
IRCT 2015 012914504N3	Wrong study design
IRCT 2016 041627412N1	Wrong study design (no adherence outcomes)
IRCT 2017 0512033932N5	Wrong study design
IRCT 2018 0207038655N1	Wrong study design - not designed to assess adherence
Jhinger 2018	Wrong study design - not designed to assess adherence (excluded those who lacked compliance to prescribed medication)
Kattamis 2018	Review
Kattamis 2021	Wrong study design - non-randomised
Kejriwal 2020	No intervention
Kidson Gerber 2008	Wrong study design - clinical audit of medication use
Kolnagou 2008	Wrong study design - medication study not RCT
Kompany 2009	Wrong study design: not designed to assess adherence
Leonard 2014	Wrong study design - single-treatment study
Loiselle 2015	Wrong study design/review/duplicate
Loiselle 2016	Review
Madmoli 2019	Wrong study design - not designed to measure adherence
Matti 2013	Wrong study design - not designed to measure compliance/adherence
Mazzone 2009	Wrong comparator - healthy children not taking iron chelation therapy
Mohamed Al Nasiri 2018	Wrong study design
Mohammadi 2018	Wrong intervention: curcumin vs placebo
Molavi 2013	Wrong study design (no assessment of adherence)
Molavi 2014	Wrong study design (no assessment of adherence)
Molazem 2016	Wrong study design (no adherence outcome)
NCT00061750	Wrong study design: not designed to measure adherence

Study	Reason for exclusion
NCT01709032	Not designed to measure adherence to iron chelation therapy
NCT02133560	Wrong study design - single-centre study with no control
NCT02466555	Wrong study design - single-centre study with no control
NCT03233269	Wrong study design
NCT03342404	Wrong intervention
NCT03381833	Wrong study design (no assessment of adherence)
NCT03591575	Wrong study design
NCT03637556	Wrong study design
NCT04092205	Wrong study design
NCT04292314	Wrong intervention
NCT04541875	No intervention
NCT04688411	Wrong intervention
Pakbaz 2005	Wrong study design - single-centre study with no control
Pantalone 2011a	Wrong study design: non RCT of medicinal trial
Patalia Abishek 2014	Wrong comparator (herbal); wrong study design (not designed to measure adherence)
Peng 2013	Wrong study design (no assessment of adherence)
Porter 2012	Wrong study design - medication intervention not a RCT
Safaei 2019	Wrong study design
Sanjeeva 2015	Wrong study design
Sebastian 2020	Wrong population (excluded those with low adherence post-randomisation); therefore wrong study design (not designed to assess adherence)
Shah 2021	Wrong study design
Shih 2020	Review
Sidhu 2021	Wrong study design - descriptive cohort
Smith 2017	Wrong study design
Souran 2019	Wrong study design - not designed to measure adherence
Tripathy 2021	Wrong study design
UMIN 000007644	Wrong study design

Study	Reason for exclusion
Vichinsky 2008	Not designed to measure adherence to iron chelation therapy
Viola 2020	Wrong study design
Vlachodimitropoulou Koumoutsea 2017	Wrong study design
Waheed 2014	Not designed to measure adherence to iron chelation therapy
Walsh 2014	Review
Wilson 2017	Wrong study design
Yarali 2006	Not designed to measure adherence to iron chelation therapy

RCT: randomised controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

Bhojak 2020

Methods	**Type of study**: RCT: randomised by chit method
Participants	Participants: children and adolescents with thalassaemia aged 3 to 18 years. Target sample size N = 30 **Inclusion criteria** 1. Diagnosed with thalassaemia major 2. Aged 3 years to 18 years 3. On regular deferasirox therapy 4. Serum ferritin more than 1000 mg/dl 5. Positive consent for study **Exclusion criteria** 1. Younger than 3 years or older than 18 years 2. Negative consent 3. Renal failure 4. Cataract 5. Ototoxicity 6. HIV positive 7. Hepatitis B positive 8. AV block 9. Asthma 10. Ongoing infection (temporary exclusion included on recovery) 11. Severe allergy
Interventions	**DFX**: oral tablet at a dose of 15 to 40 mg/kg/day every day for 6 months **DFO**: injection given at a dose of 20 to 40 mg/kg/dose 2 hours after blood transfusion once monthly for 6 months
Outcomes	**Primary outcome (6 months)**

Bhojak 2020 *(Continued)*

	Consecutive serum ferritin levels every 2 months with ongoing dosage of iron chelators **Secondary outcome (6 months)** The velocity in decreasing serum ferritin
Notes	Postgraduate thesis Date of first enrolment (India): 1 Sept 2017 **CTRI/2017/08/009441** (prospectively registered on: 22 August 2017) **Contact details** **Name**: Ratna D Bhojak **Affiliation**: 3rd Year Resident, Sir Takhtasihnji General Hospital Bhavnagar **Address**: Pediatrics Department, Sir Takhtasihnji General Hospital Campus Bhavnagar, Bhavnagar, Gujarat, 364002 India **Phone**: 7874322722 **Email**: bhojakratna.rb@gmail.com

Crosby 2019

Methods	The primary aims of this study were to examine data on MEMS bottle use among adolescents (ages 13 to 21 years) with SCD to: 1) evaluate the feasibility of MEMS bottle use; and 2) elicit barriers and facilitators to MEMS bottle use As part of a larger study of a self-management intervention, adolescents were asked to use a MEMS bottle to store and administer their daily oral medication (hydroxyurea or deferasirox) for the 18-week study duration
Participants	Adolescents (ages 13 to 21 years) with SCD
Interventions	Electronic monitoring devices (bottles with computer chips that record date- and time-stamps of device openings) such as MEMS® bottles
Outcomes	Adherence rates over time
Notes	Conference abstract only **Disclosures** Quinn: *Celgene:* Membership on an entity's Board of Directors or advisory committees; *Amgen:* Other: Research Support

CTRI/2020/07/026771

Methods	**Study design**: randomised, parallel-group study **Method of generating randomisation sequence**: computer-generated randomisation **Method of allocation concealment**: NA **Blinding and masking**: open-label

CTRI/2020/07/026771 *(Continued)*

Participants	**Target sample size:** 45 **Inclusion criteria** 1. Transfusion dependent beta-thalassaemia major 2. Aged between 10 and 18 years 3. On a single oral iron chelator (DFX) with abnormal ECHO findings **Exclusion criteria** 1. On more than 1 oral iron chelator 2. Congenital heart disease 3. Rheumatic heart disease 4. Other haemoglobinopathies like sickle cell disease 5. Chronic infections like TB, HIV, HEP-C, HEP-B 6. Raised serum transaminase levels (more than 5 times the upper normal limit) 7. History of allergy to either drug
Interventions	**Combination DFP with DFX**: oral DFP 75 mg/kg/day every 8 hours with oral DFX 30 mg/kg/day once daily for 6 months **DFX alone**: oral DFX 30 mg/kg/day once daily for 6 months
Outcomes	**Primary outcome** 1. Differences in cardiac function as assessed by echocardiography and tissue doppler imaging after 6 months treatment **Secondary outcomes** 1. Change in complete blood count parameters following 1, 2, 3, 4, 5 and 6 months treatment 2. Change in liver and kidney function parameters following 6 months treatment 3. Change in serum ferritin levels following 6 months treatment 4. Decrease in liver and spleen size as assessed by ultrasound examination following 6 months treatment
Notes	Prospective registration **Date of first enrolment**: 30 July 2020 **Last refreshed on**: 24 November 2021 (not yet recruiting) **Primary sponsor**: KAHER J N Medical College **Contact details** **Name**: Dr Neha Goudar **Affiliation**: J N Medical College **Address**: Department of Pediatrics Ground Floor, J N Medical College, JNMC Campus, Nehru Nagar, Belgaum 590010 Belgaum, KARNATAKA India **Telephone**: 9845688999 **Email**: drsmjali@gmail.com **Name**: Dr Sujata M Jali **Affiliation**: J N Medical College

CTRI/2020/07/026771 *(Continued)*

Address: Department of Pediatrics Ground Floor, J N Medical College, JNMC Campus, Nehru Nagar, Belgaum 590010 Belgaum, KARNATAKA India

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Email: drsmjali@gmail.com

Eghbali 2019

Methods	Unclear whether randomised (described as double-blinded, randomised and non-randomised in trial registration) Children with thalassaemia major referring to Amirkabir hospital in Arak are randomly divided into 2 groups of 25 people
Participants	**Inclusion criteria:** children over 5 years old (age 5 to 18 years) with thalassaemia major **Exclusion criteria:** hepatitis and HIV, kidney and liver failure
Interventions	**Group 1:** treated with the Exjade group daily 30 mg/kg single dose of morning fasting **Group 2:** in addition to Exjade, Desferal ampoule 50 mg/kg subcutaneously with Desferal pump
Outcomes	Serum ferritin levels are checked for 6 months
Notes	Study dates: 22 Sept 2016 to 22 May 2017 (recruitment complete) Ethics committee reference number IR.ARAKMU.REC.1395.220 **Registrant information** Name: Aziz Eghbali Name of organisation/entity: دانشگاه علوم پزشکی اراک Country: Iran (Islamic Republic of) Phone: +98 86 3465 5314 Email address: dr.eghbali@arakmu.ac.ir **Funding source** Vice Chancellor for Research Arak university of Medical Sciences

EUCTR 2017-003777-34-NL

Methods	**Design**: randomised, placebo-controlled, double-blind, cross-over trial (2 arms)
Participants	Target sample N = 40 **Inclusion criteria** 1. Diagnosis of hereditary anaemia: haemoglobinopathy (including all sickle cell syndromes and beta-thalassaemia), sideroblastic anaemia, congenital dyserythropoietic anaemia or an erythrocyte enzyme deficiency 2. Haemoglobin before study inclusion < 7.0 mmol/L 3. Clinically stable and relevant iron overload defined as either one of:

EUCTR 2017-003777-34-NL *(Continued)*

a. baseline LIC measurement by MRI between 3 and 15 mg Fe/g without having received iron chelation 2 months prior to entering the study; or
b. baseline LIC measurement by MRI between 3 and 15 mg Fe/g on stable chelation therapy (DFX, DFO or DFP), with documented stable dosage the preceding 2 months and no expected dose reductions or increases the next 2 years

4. Aged > 18 years and able to sign informed consent
5. Serum transferrin saturation > 0.40 once during the preceding 24 months
6. Received < 10 units of blood during the preceding 12 months
7. Expected to receive < 4 units of blood during the following 12 months
8. Not splenectomised during the preceding 24 months

Exclusion criteria

1. Pregnancy
2. Liver cirrhosis
3. Heart failure
4. Severe cardiac iron overload defined as MRI T2* < 20 ms
5. Severe liver iron overload defined as MRI LIC > 15 mg Fe/g dry weight
6. Expected poor compliance
7. Currently taking PPI and not able to stop for personal or medical reasons
8. Phlebotomised as treatment for iron overload
9. Current peptic ulcer disease, gastrointestinal bleeding or other causes of blood loss
10. Contra-indication for esomeprazole use
11. Concomitant use of clopidogrel
12. Contra-indication for MRI
13. Received > 4 units blood during one of the treatment periods of 12 months

Interventions	**Intervention**: esomeprazole (oral capsule); manufacturer Sandoz RVG 107193-4 **Control**: placebo (oral capsule)
Outcomes	**Main objective** To show that PPIs compared to placebo are an effective treatment of secondary haemochromatosis in a relative large number of participants with hereditary anaemia and mild iron overload **Primary outcomes** 1. Change in LIC from baseline (start of treatment) to 12 months measured by MRI of the liver, expressed in mg Fe/g dry weight after data analysis of the T2* and T1 images of the MRI **Secondary objectives** To assess the safety and side effects of treatment with esomeprazole. To assess quality of life during treatment with esomeprazole compared with placebo. To evaluate cost-effectiveness of esomeprazole in treatment of iron overload in hereditary anaemia. To assess the changes in 'iron markers' during treatment with esomeprazole compared with placebo. To assess the need for chelation therapy after 1 year of treatment with esomeprazole compared with placebo. To assess the adherence to therapy in a real life setting. Time point(s) of evaluation of this endpoint: 1. MRI 1: baseline; the maximum time interval between start of study medication and the baseline MRI will be 14 days 2. MRI 2: after the first treatment year (12 months); the maximum time interval between the cross-over point and the MRI will be 7 days 3. MRI 3: after the second treatment year (24 months); the maximum time interval between the end of study treatment and the MRI will be 7 days

EUCTR 2017-003777-34-NL *(Continued)*

Secondary outcomes

1. Tolerability of esomeprazole (incidence of side effects/adverse events will be monitored every 3 months during study visits; measurement of vitamin B12, zinc and magnesium at baseline, 12 months and 24 months; report of airway infections)
2. Quality of life (assessed with EQ5D-forms every 3 months)
3. Cost-effectiveness esomeprazole (assessed by a prospective cost-effectiveness analysis; IMCQ and iPCQ questionnaires every 3 months)
4. Changes in markers of iron metabolism
   a. Plasma hepcidin at baseline
   b. Serum ferritin at baseline, 12 months and 24 months
5. Compliance to study drug
   a. Plasma gastrin at baseline, 6 months, 12 months, 18 months and 24 months
   b. Counting of the capsules
6. Need for chelation therapy

Notes	Results available without subgrouping, and so cannot extract only SCD and thalassaemia data - await publication of further results Proton pump inhibition for secondary haemochromatosis in hereditary anaemia, a phase III, placebo-controlled, randomised, cross-over clinical trial - PPI Shine Again Funding: ZonMW First recruitment: 9 February 2018 Registered: 22 February 2018 Last update: 25 June 2018 (www.apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2017-003777-34-NL) **Contact details** **Name**: Van Creveldkliniek **Affiliation**: UMC Utrecht **Address**: Heidelberglaan 100 3584CX Utrecht Netherlands **Telephone**: 0031088-7558450 **Email**: vck-research@umcutrecht.nl

EX-PAT 2013

Methods	Prospective cohort study, parallel-group
Participants	Participants using DFX - we do not know the disease diagnosis and therefore awaiting classification Exclusion criteria: not stated
Interventions	Educational intervention, standard care (as defined in the study)
Outcomes	Exjade Patient Compliance Program (EX-PAT) was established to increase patients' knowledge about DFX usage. This abstract aimed to represent the results of the pilot EX-PAT programme. It is highly recommended to educate the patients under iron chelating treatment about possible complications and usage of chelating agents

EX-PAT 2013 *(Continued)*

Notes	Email sent to author asking for the following information so we could include the study: a full study report of this abstract. If this is not available would it be possible to have more information on: • the disease diagnosis of the participants (were they sickle cell (phenotypes) or thalassaemia (phenotypes) or other); • how participants were assigned to intervention or control; • any inclusion/exclusion criteria; • any group differences; • is the age range for the whole group or is it for the intervention group only? If so could we have the age range for the control group; • baseline and end of study ferritin levels; • SAEs or any AEs.

IRCT 2013 042213092N1

Methods	**Design**: unblinded, parallel RCT
Participants	Target sample size: 70 **Inclusion criteria** 1. Aged 15 to 25 years 2. HIV-negative 3. No mental illness or chronic diseases besides thalassaemia **Exclusion criteria** 1. Specific disease during the study period that stop samples 2. Inability to participate in the intervention 3. Sickle thalassaemia patients
Interventions	**Intervention group**: self-management empowerment model, booklet, 2 sections, between 1 week (to achieve the target, 5 basic and logic steps is designed. Empowerment model with the concepts of awareness of personal changes, independence, role playing, adaptation, perceived satisfaction, being in control) **Control group**: routine care, no intervention
Outcomes	Quality of life (before and 1.5 months post-intervention) Empowering score (before and 1.5 months post-intervention)
Notes	'The Effect Of Education base on Self-Management Empowering Model On The Quality Of Life In Adolescent and youth With Major Thalassemia' Funding: Research Center of Bushehr University of Medical Sciences Recruitment started: 20 June 2013 (expected end date 21 Sept 2013; ethics approval 30 Dec 2013); http://en.irct.ir/trial/13021 First enrolment: 20 June 2013; date of registration: 3 February 2014; recruitment "complete"l; last updated: 22 February 2018; https://apps.who.int/trialsearch/Trial2.aspx?TrialID=IRCT2013042213092N1 **Contact**

IRCT 2013 042213092N1 *(Continued)*

- For scientific enquiries: Dr Maryam Ravanipour, MD/MPH, Associate Professor, The Persian Gulf Tropical Medicine Research Center, Bushehr University of Medical Sciences, Bushehr, Sangi Street, Bushehr; ravanipour@bpums.ac.ir, +98 77 1455 0187
- For updating data: Najmeh Razzazan, MSc Student in Nursing, Student Research Committee, Bushehr University of Medical Sciences, najme.razazan@yahoo.com

IRCT 2016 0310026998N7

Methods	**Design**: unblinded, parallel RCT 54 eligible participants β-thalassaemia receiving DFO plus DFP will be randomly selected and randomly divided into 2 groups (27 participants in each group)
Participants	**Inclusion criteria** 1. People with β-thalassaemia receiving DFO plus DFP who have been referred to the outpatient clinic for routine blood transfusion **Exclusion criteria** 1. Hepatic impairment (ALT > 5 times more than normal) 2. Pregnancy 3. Renal impairment (GFR < 30 mL/min) 4. Chelating agent-induced renal impairment
Interventions	**Intervention group** (27 participants): DFX plus DFP **Control group** (27 participants): DFO plus DFP
Outcomes	Serum ferritin will be measured every 3 months Cardiac MRI T2 * and LIC will be measured before and after the study All participants will be evaluated with the SF-36 questionnaire for measuring quality of life before and after the study
Notes	**IRCT registration number:** IRCT20160310026998N7 **Registration date**: 5 May 2018, 1397/02/15 **Registration timing:** registered while recruiting **Last update:** 5 May 2018, 1397/02/15 **Contact details** **Name**: Saba Ghaffary **Name of organisation/entity**: Faculty of Pharmacy, Tabriz University of Medical Sciences **Country**: Iran (Islamic Republic of) **Phone**: +98 33266042 **Email address**: ghaffarys@tbzmed.ac.ir

IRCT 2019 0106042262N1

Methods	**Design**: parallel RCT, unblinded **Randomisation description**: all samples encoded by a third person that does not participate in the research, participants then divided into 2 groups by using a random digits table **Target sample size**: 108 **Actual sample sizereached:** 107
Participants	**Inclusion criteria** 1. Transfusion-dependent β-thalassaemia with ferritin > 1000 2. Not treated with combination iron chelators 3. With heart and liver iron load 4. Normal liver and renal function 5. Aged over 10 years **Exclusion criteria** 1. Gastrointestinal problem before research
Interventions	**Intervention group**: DFX 20 - 40 mg/kg daily (this study uses Osveral 125 mg, 250 mg and 500 mg formulations produced by the Osvah Company of Iran) plus DFP 15 mg/kg/dose in 3 doses (produced by the Avicenna Company of Iran) for 6 months **Control group**: DFO (vial 500 mg) 20 to 50 mg/kg daily 3 infusions with a pump and DFP 15 mg/kg/dose in 3 doses (produced by the Avicenna Company of Iran) for 6 months
Outcomes	**Primary outcomes** 1. Heart iron concentration at baseline and 6 months measured by MRI T2* 2. LIC at baseline and 6 months measured by MRI T2* **Secondary outcome** Serum ferritin level at baseline, 3 months and 6 months
Notes	**Recruitment status:** recruitment complete **Contact details** **Name**: Ali Reza Fazeli Varzaneh **Country**: Iran (Islamic Republic of) **Phone**: +98 31 3527 6082 **Email address**: rezaali.fazeli6768@gmail.com

IRCT 2019 0827044634N1

Methods	**Design**: single-blind, placebo-controlled RCT, parallel design **Randomisation description**: random allocation of the samples to the study groups will be based on days of visit to the clinic (couple and individual) and on a lottery basis **Blinding description**: the statistical analyst will be unaware of the intervention and control groups Target sample size: 60

IRCT 2019 0827044634N1 *(Continued)*

	The number of adolescents in the present study age range in the Sarver centre is 63 people
Participants	**Inclusion criteria** 1. Adolescents with β-thalassaemia major aged 14 to 18 years 2. Minimum elementary (primary) education 3. No other chronic comorbidities **Exclusion criteria** 1. Unwillingness to participate in the study 2. Other chronic comorbidities 3. Passing similar courses of hope therapy
Interventions	**Intervention group:** the Hope Therapy programme will be conducted in 8 sessions of 60 minutes (2 sessions/week) based on Snyder studies and each session will consist of 4 sections. In the first part, about 10 minutes will be discussed of clients' activities and assignments in the last week and encourage people to help each other with problems related to those assignments. In the second part, they will learn about 10 minutes of mental training and hope-related skills that fall into 3 areas of crossroads and operating goals. The third part, which will take about 30 minutes, will discuss how to apply these skills in daily life, and will encourage clients to objectively and explicitly help one another with the use of hope skills, to solve them. In the final 10 minutes of the session, participants will be given an assignment on the topic of the same session, and in the next session before the session begins, the assignments will be reviewed and with the participation of the group members will discuss assignments. **Control group:** only routine care will be provided for the control group
Outcomes	**Primary outcomes** 1. Adherence to treatment assessed at baseline, immediately and 1 month after the intervention measured using a score obtained from Modanloo treatment adherence questionnaire 2. Hope assessed at baseline, immediately and 1 month after the intervention measured using a score obtained from Snyder Hope Questionnaire
Notes	**IRCT registration number:** IRCT20190827044634N1 **Registration date:** 1 November 2019, 1398/08/10 **Registration timing**: registered while recruiting **Last update:** 1 November 2019, 1398/08/10 **Registration date:** 1 November 2019, 1398/08/10 **Contact details** **Name of organisation/entity**: Mashhad University of Medical Sciences **Full name of responsible person**: Saeedeh Ilkhani **Position**: postgraduate student **Street address**: No. 97, vahdate eslami 8., Bist Metri Ave, Emam Khomeini Blvd City Torbate jam Province Razavi Khorasan Postal code 9148837663 **Phone**: +98 51 5252 7790 **Email**: ilkhanis1@mums.ac.ir

IRCT 2020 0126046270N1

Methods	Semi-experimental pre-test post-test, with intervention and control groups, available sampling Not randomised or blinded, parallel assignment
Participants	**Inclusion criteria** 1. Thalassaemia major 2. Age range 18 to 8 years 3. Family satisfaction with continuous participation in training sessions 4. No history of neurological and psychological illness and no psychological treatment 5. No drug abuse
Interventions	**Intervention group:** participants trained by the researcher for 10 weeks, 60-minute weekly sessions including the first session introducing participants and the Friends programme F: Introducing feelings Relationship between thoughts and feelings R: How to feel good and relaxed I: Developing Positive Thoughts Introducing Good Thoughts and Unhelpful Thoughts, Attention Training E: Exploring Solutions and Plans for Coping Stage Session Fifth Session Problem N: Reward Yourself Now! D: Don't Forget Practice: S Smile! Eighth session of generalisation of Friends skills in different difficult situations The ninth session of questionnaires and gratitude and thanksgiving and the 10th session of questionnaire completion 1 month after the completion of the programme **Control group:** as a comparison group, there is no intervention, only pre-test
Outcomes	**Primary outcome** 1. "Anxiety Score in Multidimensional Anxiety Questionnaire" measured at baseline, immediately after the study and 30 days after the intervention 2. "The Loneliness Score in the Asher Child Loneliness Questionnaire" measured at baseline, immediately after the study and 30 days after the intervention
Notes	**IRCT registration number:** IRCT20200126046270N1 **Registration date:** 25 February 2020, 1398/12/06 **Registration timing:** retrospective **Last update:** 25 February 2020, 1398/12/06 **Recruitment status**: recruitment complete **Contact details** **Name**: Masoumeh Ghorbanpoor **Country**: Iran (Islamic Republic of) **Phone**: +98 17 3358 8226

IRCT 2020 0126046270N1 *(Continued)*

Email address: ghorbanpoor8793@gmail.com

IRCT 2020 0606047670N2021

Methods	**Design**: quasi-RCT with a control group, without blinding **Target sample size:** 34 **Randomisation description**: sampling method will be done randomly and using a lottery among eligible participants. In this way, the number will be written in the number of sample units and placed in a bag, and participants who choose odd numbers will be in the intervention group and patients who choose an even number will be in the control group.
Participants	**Inclusion criteria** 1. Aged between 15 and 20 2. Willingness to participate in the study 3. Have undergone blood transfusion at least once every 6 months and at least once a week 4. Having a thalassaemia medical record 5. Have a minimum literacy **Exclusion criteria** 1. Severe and chronic diseases such as cancer that cannot be studied 2. Drug addiction (false impact on research units) 3. Severe mental illness and severe frustration
Interventions	**Intervention group**: spiritual care training in 6 sessions of 45 to 60 minutes in groups and in 3 weeks in the morning shift. The content of spiritual care education will be prepared with the focus on topics such as trust, recourse, patience, prayer, supplication and prayer, self-knowledge, communication with God always, reconciliation with people and communication with others **Control group:** no intervention for the control group and they will receive their routine care as before. (Counselling by the centre itself, which is usually done once a month and has no effect on the study)
Outcomes	**Outcomes** 1. Life expectancy score in Schneider life-expectancy questionnaire, measured at the beginning of the study (before the intervention) and 35 days later (3 weeks of the intervention and 2 weeks after) 2. Spiritual health score in Pultezin spiritual health questionnaire, measured at the beginning of the study (before the intervention) and 35 days later (3 weeks of the intervention and 2 weeks after)
Notes	**IRCT registration number:** IRCT20200606047670N2 **Registration date:** 8 January 2021, 1399/10/19 **Registration timing**: registered while recruiting **Last update:** 8 January 2021, 1399/10/19 **Recruitment status**: recruitment complete **Contact details** **Name**: Sadegh Dehghanmehr **Country**: Iran (Islamic Republic of)

IRCT 2020 0606047670N2021 *(Continued)*

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NCT00004982

Methods	RCT, parallel-group
Participants	**Inclusion criteria** 1. Aged 7 years and older (child, adult, senior) 2. Either gender 3. Iron overload **Exclusion criteria** 1. Overt cardiac disease
Interventions	**Intervention**: combination iron chelation therapy (several combinations of experimental iron chelating drugs are being used) **Control**: standard care (as defined in the trial)
Outcomes	No specific outcomes listed This small trial is testing the premise that a combination of drugs as a new approach to iron chelation therapy may reduce side effects and increase efficacy. If both drugs can be given orally, there may be a better chance of finding a suitable alternative to Desferal. Several combinations of experimental iron chelating drugs are being used in this trial.
Notes	This trial has been completed **Sponsor**: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). No study results posted. NCT00004982: scant information about the trial was documented on the clinicaltrials.gov website. We have been unable to identify any publications from this trial and despite repeated emails to the trial co-ordinator and searching the funder's website, we have been unable to identify any further details about the trial. Start date: December 1998; estimated completion November 2002

AEs: adverse events
ALT: alanine aminotransferase
DFO: deferoxamine
DFP: deferiprone
DFX: deferasirox
GFR: glomerular filtration rate
HEP: hepatitis
IMCQ: iMedical Consumption Questionnaire
iPCQ: iProductivity Cost Questionnaire
LIC: liver iron concentration
MRI: magnetic resonance imaging
PPI: proton pump inhibitors
RCT: randomised controlled trial
SAEs: serious adverse events
SCD: sickle cell disease
SF-36: Short-form 36
TB: tuberculosis

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

CALYPSO

Study name	'Trial to evaluate treatment compliance, efficacy and safety of an improved DFX formulation (granules) in children (2- < 18 years old) with iron overload'
Methods	**Design**: RCT, parallel-group Participants were randomised 1:1 to DFX granules or DT for 48 weeks, stratified by age group and prior iron chelation therapy Parents/guardians provided written informed consent
Participants	**Inclusion criteria** • Written informed consent/assent before any study-specific procedures; consent will be obtained from parent(s) or legal guardians. Investigators will also obtain assent of patients according to local guidelines • Boys and girls aged ≥ 2 and < 18 years • Any transfusion-dependent anaemia associated with iron overload requiring iron chelation therapy and with a history of transfusion of approximately 20 packed RBC units and a treatment goal to reduce iron burden (300 mL packed RBC = 1 unit in adults whereas 4 mL/kg packed RBC is considered 1 unit for children) • SF > 1000 ng/mL, measured at screening visit 1 and screening visit 2 (the mean value will be used for eligibility criteria) **Exclusion criteria** • Creatinine clearance below the contraindication limit in the locally approved prescribing information. Creatinine clearance will be estimated from serum creatinine (using the Schwartz formula) at screening visit 1 and screening visit 2 and the mean value will be used for eligibility criteria. • Serum creatinine > 1.5 x ULN at screening measured at screening visit 1 and screening visit 2 (the mean value will be used for eligibility criteria) • ALT and/or AST > 3.0 x ULN (criterion no longer applicable, removed as part of amendment 1) • Prior iron chelation therapy • Liver disease with severity of Child-Pugh class B or C • Significant proteinuria as indicated by a urinary protein/creatinine ratio > 0.5 mg/mg in a non-first void urine sample at screening visit 1 or screening visit 2 • Significant impaired GI function or GI disease that may significantly alter the absorption of oral DFX (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhoea, malabsorption syndrome or small bowel resection)
Interventions	**Intervention**: DFX granule formulation, iron chelation-naive participants started on 14 mg/kg/day, adjusted after 4 weeks as needed; pre-treated participants received a starting dose corresponding to their closest pre-washout dose, adjusted every 3 months as needed **Comparator**: DFX DT formulation iron chelation-naive participants started on 20 mg/kg/day, adjusted after 4 weeks as needed; pre-treated participants received a starting dose corresponding to their closest pre-washout dose, adjusted every 3 months as needed
Outcomes	**Primary outcome measures** • Compliance • Change in SF in iron chelation therapy-naive participants **Secondary outcome measures** • Domain scores of treatment satisfaction and palatability over time • Overall safety, as measured by frequency and severity of AEs (including active monitoring for renal toxicity and renal failure; hepatic toxicity and hepatic failure; and gastrointestinal haemorrhage)

CALYPSO *(Continued)*

	• Changes in laboratory values from baseline (serum creatinine, creatinine clearance, ALT, AST, RBCs and WBC) • Vital signs, physical, ophthalmological, audiometric, cardiac, and growth and development evaluations • Rate of dosing instructions deviations ('Compliance', using a questionnaire) • Pre-dose DFX concentrations in all participants (pre-dose PK data from all participants will be analysed to support the assessment of compliance) • Post-dose DFX concentrations between 2 and 4 hours post-dose • Change in SF in iron chelation therapy-naive and pre-treated participants PK/PD relationship to explore exposure-response relationships for measures of safety and effectiveness: serum creatinine change from baseline, notable serum creatinine values, serum creatinine clearance change from baseline and notable serum creatinine clearance categories, SF change from baseline, in relationship to derived PK parameters for pre- and post-dose DFX concentrations Assess additional safety, as measured by frequency and severity of adverse for granules during extension phase includes active monitoring for renal toxicity; including renal failure, hepatic toxicity; including hepatic failure, and gastrointestinal haemorrhage, and changes in laboratory values from baseline (serum creatinine, creatinine clearance, ALT, AST, RBC and WBC). In addition, vital signs, physical, ophthalmological, audiometric, and growth and development evaluations will be assessed
Starting date	21 October 2015
Contact information	**Sponsors and Collaborators:** Novartis Pharmaceuticals **Central Contact Person:** Novartis Pharmaceuticals **Telephone:** 1-888-669-6682 **Central Contact Backup:** Novartis Pharmaceuticals **Study Officials:** Novartis Pharmaceuticals **Study Director:** Novartis Pharmaceuticals **Principal Location:** United States, Pennsylvania **Principal Investigator**: Janet L. Kwiatkowskil **Institution:** Children's Hospital of Philadelphia Onc. Dept **Email Contact:** John Hammond 267-426-5602, hammondjh@email.chop.edu **Address:** Children's Hospital of Philadelphia, Oncology Dept, Philadelphia, Pennsylvania, USA, 19104-4399
Notes	NCT02435212 **Other study ID numbers:** CICL670F2202 2013-004739-55 (EudraCT Number) Novartis Pharmaceuticals|NovartisOther IDs: CICL670F2202|2013-004739-55 **Recruitment status:** active, not recruiting **Actual primary completion date:** 31 May 2018 **Estimated study completion date:** 19 December 2023 **Certification/extension first submitted:** 16 July 2018

CALYPSO *(Continued)*

	Countries: Belgium, Bulgaria, Egypt, France, Hungary, India, Italy, Lebanon, Malaysia, Oman, Panama, Philippines, Russian Federation, Thailand, Tunisia, Turkey, United States

IRCT 2015 101218603N2

Study name	'To assess compliance, efficacy and satisfaction with two different formulation of DFX in people with transfusion-dependent beta-thalassaemia'
Methods	**Design**: RCT, parallel-group
Participants	**Inclusion criteria** • Signed informed consent • Male or female aged ≥ 2 years at screening • Transfusion-dependent thalassaemia major • Regular transfusion indicated by a blood requirement ≥ 8 blood transfusions per year at screening **Exclusion criteria** • Mean levels of ALT above 5-fold the ULN • Serum creatinine above ULN • Significant proteinuria as indicated by a urinary protein/creatinine ratio > 0.6 (mg/mg) • Creatinine clearance ≤ 60 mL/min • Chronic hepatitis B infection • Active hepatitis C infection • Pregnancy or breastfeeding • Non-transfusion dependent thalassaemia
Interventions	**Intervention**: DFX (new formulation Jadenu) 14 to 28 mg/kg/day orally once daily. Dose dependent on SF level - if SF level 1000 to 1500, 14 mg/kg Jadenu; if SF level 1500 to 2000, 21 mg/kg Jadenu; and if SF level > 2000, 28 mg/kg Jadenu **Comparator**: DFX (Exjade) 20 to 40 mg/kg/day orally once daily. Dose dependent on SF level - if SF level 1000 to 1500, 20 mg/kg EXJADE; if SF level 1500 to 2000, 30 mg/kg EXJADE; and if SF level > 2000, 40 mg/kg EXJADE
Outcomes	• Participants compliance and satisfaction measured at 3 months using a questionnaire to assess participant compliance and satisfaction • SF levels • Safety; • Possible GI side effects, including diarrhoea, and dermatologic symptoms
Starting date	22 December 2015
Contact information	**Sponsor**: Dr. Seyed Basir Hashemi, Vice chancellor of research, Shiaz Univeisity of Medical Sciences **Country**: Iran **Setting**: multicentre (outpatient) **Contact**: Dr. Sezaneh Haghpanah **Institution**: Hematology Research Center, Nemazee Hospital, Shiraz, Iran **Email**: haghpanah@sums.ac.ir

IRCT 2015 101218603N2 *(Continued)*

	Address: Dr Sezaneh Haghpan Professor of community medicine Hematology Research Center, Nemazee Hospital, Zand Street, Shiraz, Iran
Notes	

Madderom 2016 (TEAM study)

Study name	'A randomised controlled trial studying the effectiveness of group medical appointments on self-efficacy and adherence in SCD (TEAM study): study protocol'
Methods	**Design**: RCT, parallel-group, 3-year duration
Participants	**Inclusion criteria** • Homozygous or compound heterozygous SCD • Individuals of all ages and parents of eligible children • Informed (parental) consent **Exclusion criteria** • Individuals with a first visit to the outpatient clinic • Unable to communicate adequately due to language difficulties and/or hearing problems • Behavioural problems that will limit group functioning
Interventions	**Intervention**: over the 3-year trial, every other individual appointment will be replaced with a group medical appointment (with a total of 4 group medical appointments). A group medical appointment is a novel form of outpatient contact incorporating an individual appointment within a group consultation, in the presence of fellow patients and other medical professionals. Within a group medical appointment, more time is available for discussion on disease-related topics. In addition, information and social support from fellow patients can improve self-management and QoL. **Comparator**: individual medical appointments and standard care
Outcomes	Primary and secondary endpoints will be measured at baseline (start of the study), after 1.5 years (after 2 group medical appointments) and after 3 years (after 4 group medical appointments), in both groups. Assessments are performed at the hospital, directly before the outpatient visit and in presence of a psychologist. **Primary outcome** • Self-efficacy as measured by the validated Sickle Cell Self-Efficacy Scale **Secondary outcomes** • Adherence to prescribed treatment by (paediatric) haematologist • QoL as measured with the validated Pediatric Quality of Life Inventory for children and SF-36 for adults • Emergency visits and hospital admissions for SCD related symptoms and complications • Satisfaction with treating physician and nurse (by visual analogue scale: score 1 to 10) • Measurement of costs and effects in the group medical appointment and individual medical appointment groups by an economic analysis according to Dutch guidelines and with respect to an increase in self-efficacy
Starting date	The trial opened to recruitment in January 2013 for the children and in September 2015 for the adults and is still ongoing Recruitment status is given as "Suspended, trial finished", closed 1 September 2017

Madderom 2016 (TEAM study) *(Continued)*

	No publications noted as of 28 October 2021
Contact information	**Name**: Marjon H. Cnossen **Institution**: Department of Pediatric Hematology, Erasmus University Medical Center - Sophia Children's Hospital **Email**: m.cnossen@erasmusmc.nl **Address**: Department of Pediatric Hematology, Erasmus University Medical Center - Sophia Children's Hospital, Wytemaweg 80, PO Box 2060, 3000 CB Rotterdam, The Netherlands
Notes	Trial registration: NTR4750 (NL42182.000.12)

NCT04877054

Study name	'Pilot evaluation of a motivational interviewing intervention targeting adherence behaviors in youth with sickle cell disease'
Methods	**Design**: parallel RCT (open-label) Participants will be randomised 2:1 to the intervention versus an education-only control
Participants	**Inclusion criteria** • Aged 13 to 22 years with SCD as well as primary caregivers of 0- to 22-year-old SCD patients ("parents"). The lower age limit for patients' participation in their own intervention sessions was selected based on previous studies documenting MI effectiveness with adolescents as young as 13 years of age. The upper limit was selected based on the recruitment site's (JHACH) patient population. • Able to speak and understand spoken English because MI is language-dependent • SCD regimen must include at least 1 of the following medications: hydroxyurea, Endari, Adakveo or Oxbryta Patients who meet inclusion criteria may participate even if their parent chooses not to do so, although only with parental consent if 13 to 17 years old. Likewise, parents of patients may participate even if the adolescent/young adult declines their own participation, as long as they assent/consent to medical chart review. Adults (18 to 22 years of age) will not require parental consent and may choose to participate with or without a parent. **Exclusion criteria** • Cognitive, motor or language delays, as observed by research personnel or documented in the medical record, if delays preclude informed consent and/or study completion. Participants may request that research personnel read all assessment, education and intervention materials aloud in a structured interview format, in which case participants could respond to items verbally and/or by pointing to visual aids. Because of this option, participants' ability to read and write are not requirements for participation. • Because the MI component of the intervention is language-dependent and requires significant time and training for certification in another language, non-English speaking patients will only be included in this study if the psychology postdoctoral fellow hired in this study is a native Spanish speaker and can demonstrate MI proficiency in Spanish. • Participants who score in the clinically significant range (t-scores 2 standard deviations above the mean) on any of the PROMIS measures assessing depression and anxiety will be removed from the study and provided mental health resources
Interventions	**Intervention**: adherence treatment programme: 4 telehealth sessions including a combination of psycho/medical education plus a motivational interviewing component. Sessions will occur ~once

NCT04877054 *(Continued)*	
	per week, with all 4 sessions being completed within 4 to 8 weeks. Each session will include an education and MI component. **Comparator**: education only; a single education-only telehealth session including medication purpose and adherence strategy recommendations. The education session will occur via telephone or telehealth.
Outcomes	**Primary outcome measures** • Change in SCD medication adherence measured at baseline, postintervention (weeks 4 to 8 after enrolment), and 16 to 20 weeks after completion • Intervention feasibility as assessed by the fidelity rating measured postintervention (weeks 4 to 8 after enrolment) • Intervention acceptability as assessed by the Abbreviated Acceptability Rating Profile measured postintervention (weeks 4 to 8 after enrolment)
Starting date	30 December 2021
Contact information	**Contact**: Dianna M Boone, Ph.D. tel: 727-767-3206 **Email**: dboone10@jhmi.edu **Responsible party**: Johns Hopkins All Children's Hospital **Locations**: USA (Florida and Johns Hopkins All Children's Hospital) *Recruiting* Saint Petersburg, Florida, United States, 33701 **Contact**: Melissa A Faith, Ph.D. 727-767-3793 **Email**: mfaith1@jhmi.edu
Notes	First posted: 7 May 2021 Recruiting/ongoing (last update 14 January 2022) Estimated completion date: 10 May 2024 Other study ID numbers: IRB00285183

AEs: adverse events
ALT: alanine transaminase
ANC: absolute neutrophil count
AST: aspartate transaminase
CBC: complete blood count
DFO: deferoxamine
DFP: deferiprone
DFX: deferasirox
DT: dispersible tablet
GI: gastrointestinal
HPLC: high-performance liquid chromatography
LIC: liver iron concentration
LPI: labile plasma iron
MI: motivational interviewing
MRI: magnetic resonance imaging
PK/PD: pharmacokinetic/pharmacodynamic
PROMIS: Patient-Reported Outcomes Measurement Information System
QoL: quality of life
RBCs: red blood cells

RCT: randomised controlled trial
SAEs: serious adverse events
SCD: sickle cell disease
SF: serum ferritin
TSAT: transferrin saturation
ULN: upper limit of normal
WBC: white blood cell

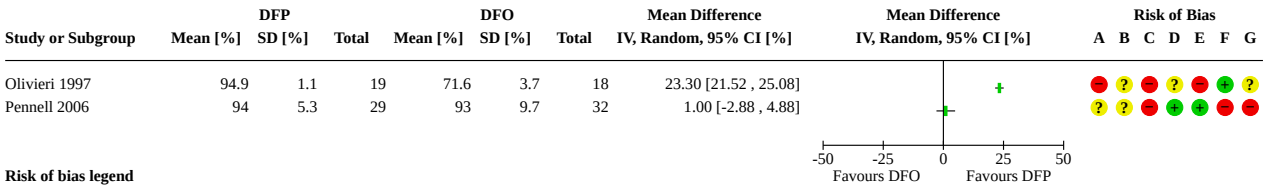
DATA AND ANALYSES

Comparison 1. DFP versus DFO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Adherence to iron chelation therapy (%, SD)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.2 Total SAEs (from therapy, disease, non-adherence)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.2.1 Total reported SAEs	1	228	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.83, 2.46]
1.3 Other SAEs (from therapy, disease, non-adherence)	2		Risk Ratio (M-H, Random, 99% CI)	Subtotals only
1.3.1 Agranulocytosis	1	88	Risk Ratio (M-H, Random, 99% CI)	7.88 [0.18, 352.39]
1.3.2 Pain crisis	1	228	Risk Ratio (M-H, Random, 99% CI)	1.30 [0.54, 3.16]
1.3.3 Acute chest syndrome	1	228	Risk Ratio (M-H, Random, 99% CI)	3.52 [0.07, 170.19]
1.3.4 Hepatic sequestration	1	228	Risk Ratio (M-H, Random, 99% CI)	1.51 [0.02, 99.77]
1.3.5 Chelation therapy-related SAEs	1	228	Risk Ratio (M-H, Random, 99% CI)	1.50 [0.28, 8.04]
1.4 All-cause mortality	3	376	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.18, 1.21]
1.4.1 Sickle cell disease	2	288	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.12, 2.02]
1.4.2 Thalassaemia intermedia	1	88	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.12, 1.63]
1.5 Iron overload: defined as proportion of participants with serum ferritin ≥ 800 (µg/L)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 Organ damage	2		Risk Ratio (M-H, Random, 99% CI)	Subtotals only
1.6.1 Liver damage	2	148	Risk Ratio (M-H, Random, 99% CI)	5.13 [0.54, 48.40]
1.7 AEs related to iron chelation	4		Risk Ratio (M-H, Random, 99% CI)	Subtotals only
1.7.1 Risk of leukopenia, neutropenia and/or agranulocytosis	3	192	Risk Ratio (M-H, Random, 99% CI)	3.95 [0.37, 41.87]
1.7.2 Risk of pain or swelling in joints	3	192	Risk Ratio (M-H, Random, 99% CI)	3.55 [0.49, 25.81]
1.7.3 Risk of nausea/vomiting	2	132	Risk Ratio (M-H, Random, 99% CI)	13.68 [0.99, 188.88]
1.7.4 Risk of increased liver transaminase	1	44	Risk Ratio (M-H, Random, 99% CI)	1.10 [0.03, 38.47]
1.7.5 Local reactions at infusion site	1	88	Risk Ratio (M-H, Random, 99% CI)	0.17 [0.00, 9.12]
1.7.6 Other AEs related to iron chelation	1	228	Risk Ratio (M-H, Random, 99% CI)	1.28 [0.81, 2.02]

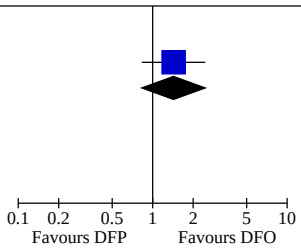
Analysis 1.1. Comparison 1: DFP versus DFO, Outcome 1: Adherence to iron chelation therapy (%, SD)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias): All outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: DFP versus DFO, Outcome 2: Total SAEs (from therapy, disease, non-adherence)

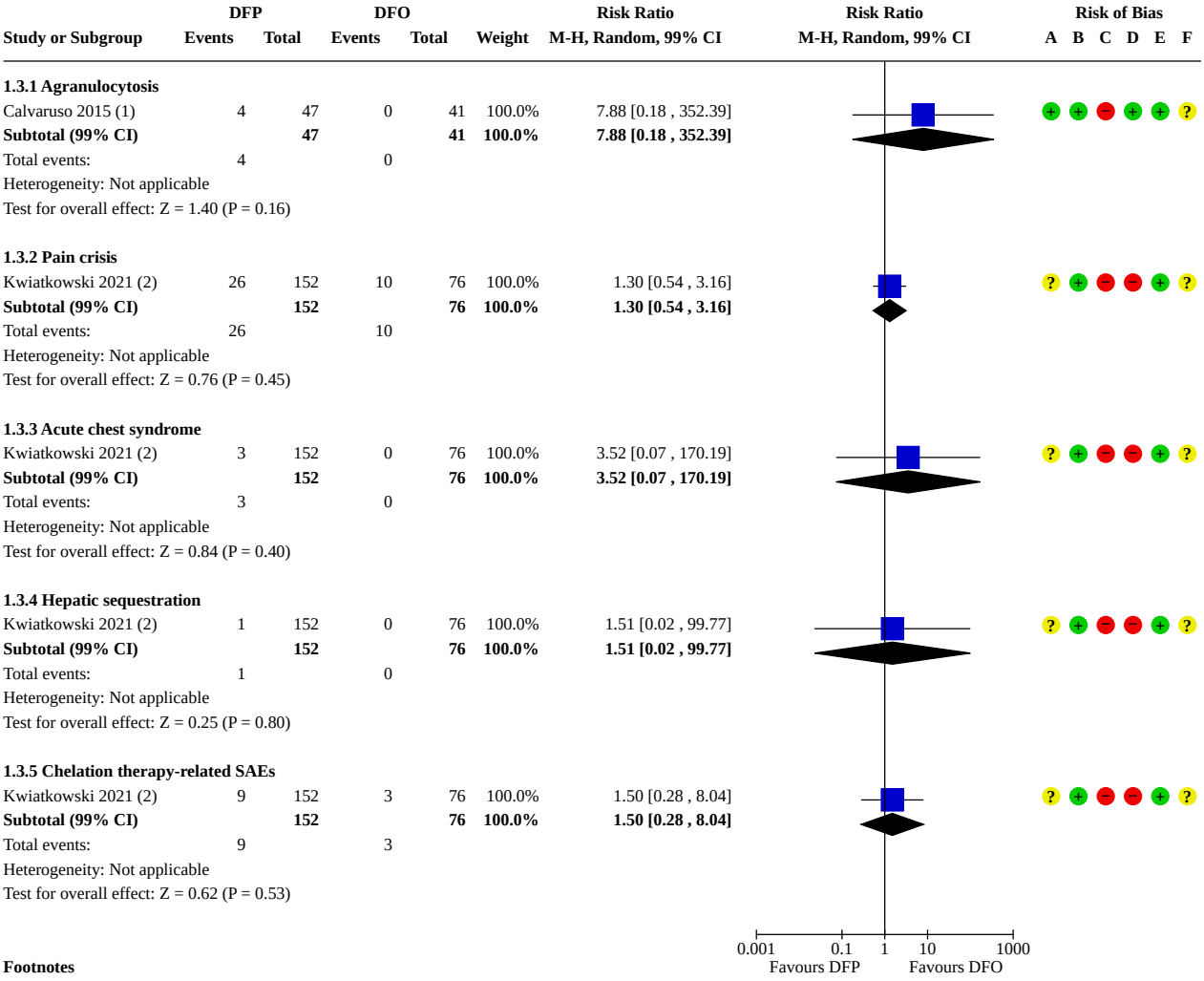
Study or Subgroup	DFP Events	DFP Total	DFO Events	DFO Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Total reported SAEs						
Kwiatkowski 2021 (1)	40	152	14	76	100.0%	1.43 [0.83 , 2.46]
Subtotal (95% CI)		**152**		**76**	**100.0%**	**1.43 [0.83 , 2.46]**
Total events:	40		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						



Footnotes
(1) 12 months

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 1.3. Comparison 1: DFP versus DFO, Outcome 3: Other SAEs (from therapy, disease, non-adherence)



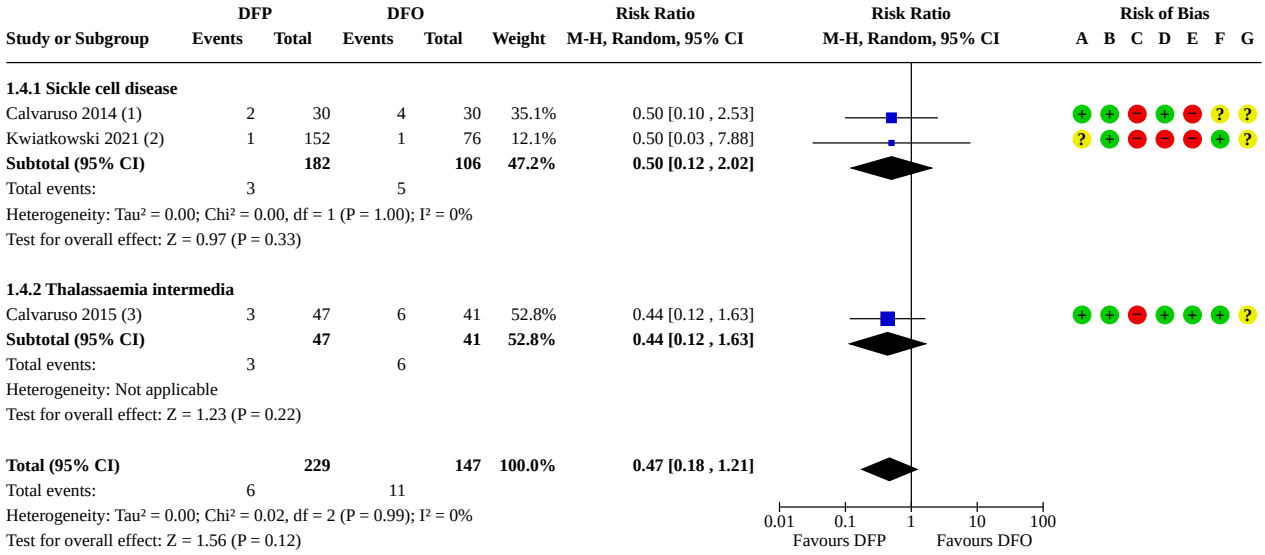
Footnotes

(1) 10 years, thalassaemia intermedia
(2) 12 months

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 1.4. Comparison 1: DFP versus DFO, Outcome 4: All-cause mortality



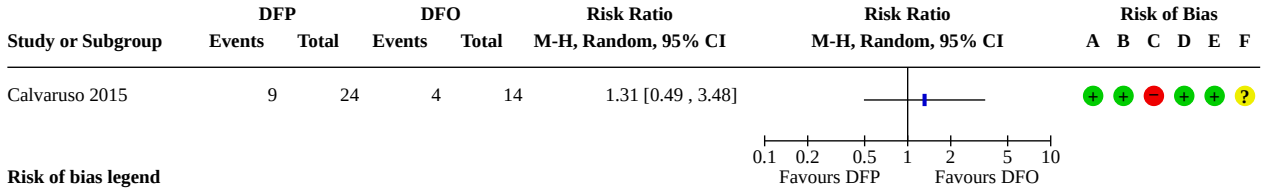
Footnotes

(1) 5 years, sickle cell disease
(2) 12 months, sickle cell disease
(3) 10 years, thalassaemia intermedia

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias): All outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.5. Comparison 1: DFP versus DFO, Outcome 5: Iron overload: defined as proportion of participants with serum ferritin ≥ 800 (µg/L)



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

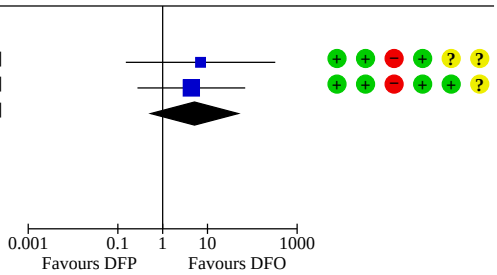
Analysis 1.6. Comparison 1: DFP versus DFO, Outcome 6: Organ damage

Study or Subgroup	DFP Events	DFP Total	DFO Events	DFO Total	Weight	Risk Ratio M-H, Random, 99% CI
1.6.1 Liver damage						
Calvaruso 2014 (1)	3	30	0	30	34.2%	7.00 [0.15 , 325.33]
Calvaruso 2015 (1)	5	47	1	41	65.8%	4.36 [0.27 , 69.43]
Subtotal (99% CI)		**77**		**71**	**100.0%**	**5.13 [0.54 , 48.40]**
Total events:	8		1			

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%

Test for overall effect: Z = 1.88 (P = 0.06)

Test for subgroup differences: Not applicable



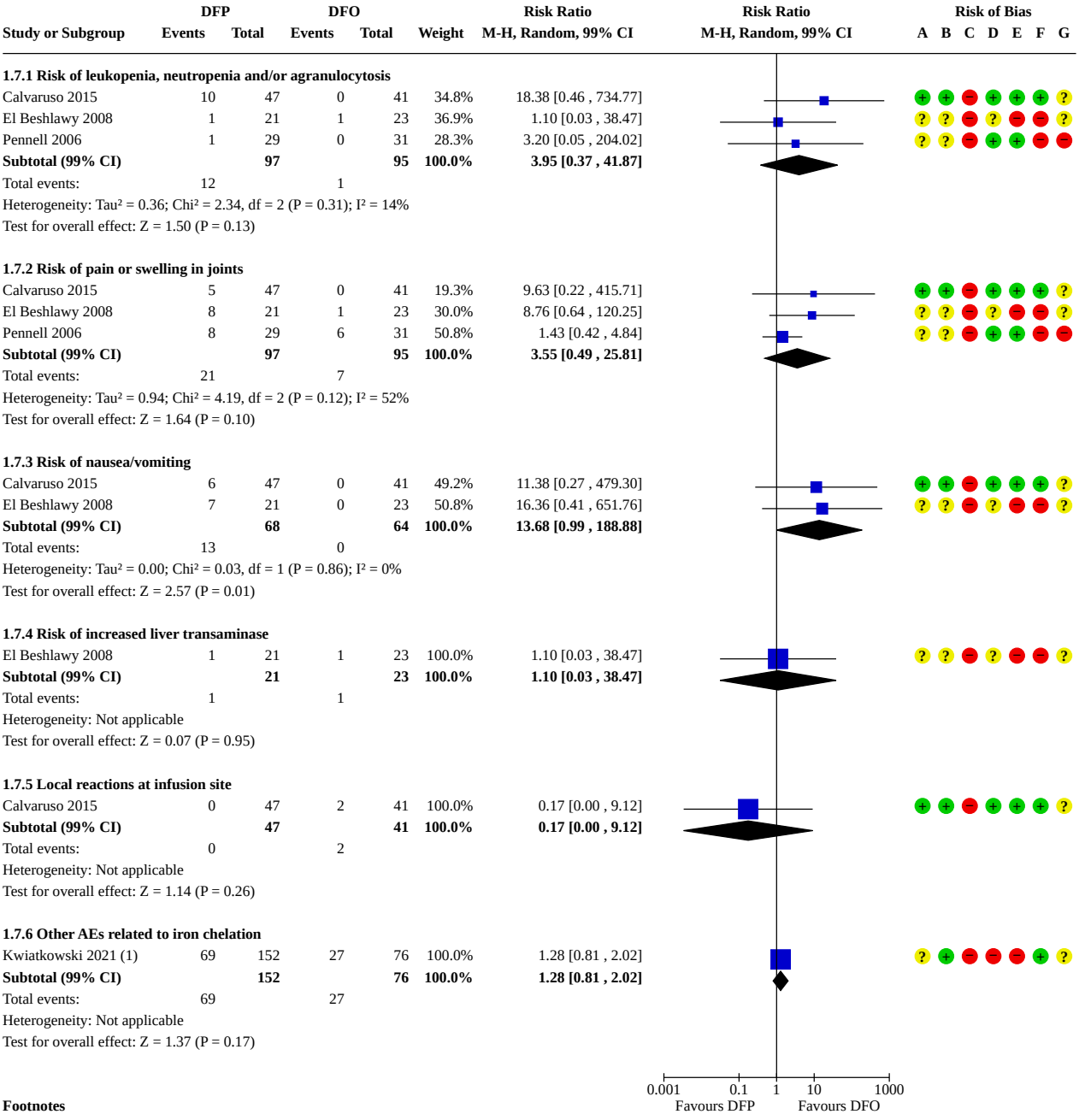
Footnotes

(1) liver damage defined as ALT at least twice the upper limit of normal

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 1.7. Comparison 1: DFP versus DFO, Outcome 7: AEs related to iron chelation



Footnotes

(1) 12 months

Risk of bias legend

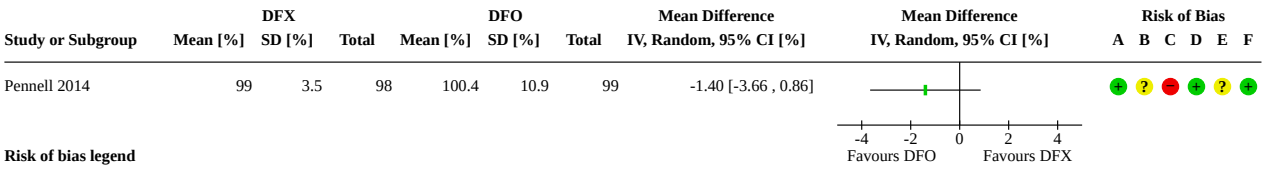
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias): All outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2. DFX versus DFO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Adherence to iron chelation therapy (%, SD)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.2 SAEs (thalassaemia)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.2.1 Total thalassaemia-related SAEs	2	247	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.41, 2.17]
2.3 SAEs (sickle cell disease)	1		Risk Ratio (M-H, Random, 99% CI)	Subtotals only
2.3.1 Painful crisis	1	195	Risk Ratio (M-H, Random, 99% CI)	1.05 [0.59, 1.86]
2.3.2 Other sickle cell disease-related SAEs	1	195	Risk Ratio (M-H, Random, 99% CI)	1.08 [0.69, 1.68]
2.4 All-cause mortality (thalassaemia)	2	240	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.06, 15.42]
2.5 Proportion of participants with iron overload (thalassaemia)	2		Risk Ratio (M-H, Random, 99% CI)	Subtotals only
2.5.1 Iron overload defined by ferritin 1500 (µg/l) or higher (thalassaemia)	1	60	Risk Ratio (M-H, Random, 99% CI)	1.18 [0.52, 2.68]
2.5.2 Proportion with severe iron overload (liver iron concentration at least 15 mg/Fe/g dry weight)	1	172	Risk Ratio (M-H, Random, 99% CI)	1.00 [0.78, 1.27]
2.5.3 Myocardial T2* < 10 ms	1	172	Risk Ratio (M-H, Random, 99% CI)	1.10 [0.62, 1.95]
2.6 Total AEs related to iron chelation - (thalassaemia)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.6.1 Total chelation-related AEs	1	187	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.76, 1.73]
2.7 Other AEs related to iron chelation - (thalassaemia)	2		Risk Ratio (M-H, Random, 99% CI)	Subtotals only
2.7.1 Gastrointestinal upset	1	60	Risk Ratio (M-H, Random, 99% CI)	3.00 [0.41, 22.06]
2.7.2 Rash	2	247	Risk Ratio (M-H, Random, 99% CI)	3.05 [0.69, 13.51]
2.7.3 Risk of increased blood creatinine	1	187	Risk Ratio (M-H, Random, 99% CI)	3.79 [0.51, 28.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.7.4 Risk of proteinuria	1	187	Risk Ratio (M-H, Random, 99% CI)	2.21 [0.39, 12.56]
2.7.5 Risk of increased ALT	1	187	Risk Ratio (M-H, Random, 99% CI)	5.69 [0.36, 89.55]
2.7.6 Risk of increased AST	1	187	Risk Ratio (M-H, Random, 99% CI)	5.69 [0.36, 89.55]
2.7.7 Risk of diarrhoea	1	187	Risk Ratio (M-H, Random, 99% CI)	5.69 [0.36, 89.55]
2.7.8 Risk of vomiting	1	187	Risk Ratio (M-H, Random, 99% CI)	6.64 [0.14, 320.28]
2.8 Total AEs (thalassaemia)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.9 Other AEs related to iron chelation (SCD)	1		Risk Ratio (M-H, Random, 99% CI)	Subtotals only
2.9.1 Risk of increased ALT	1	195	Risk Ratio (M-H, Random, 99% CI)	5.29 [0.12, 232.98]
2.9.2 incidence of abdominal pain	1	195	Risk Ratio (M-H, Random, 99% CI)	1.91 [0.80, 4.58]
2.9.3 Risk of pain or swelling in joints	1	195	Risk Ratio (M-H, Random, 99% CI)	1.06 [0.41, 2.76]
2.9.4 Risk of diarrhoea	1	195	Risk Ratio (M-H, Random, 99% CI)	4.14 [0.90, 18.92]
2.9.5 Nausea/vomiting	1	195	Risk Ratio (M-H, Random, 99% CI)	1.63 [0.90, 2.94]

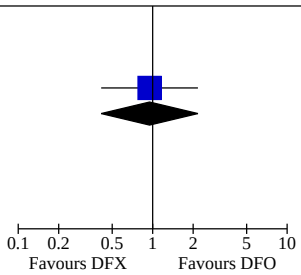
Analysis 2.1. Comparison 2: DFX versus DFO, Outcome 1: Adherence to iron chelation therapy (%, SD)

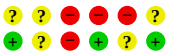


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 2.2. Comparison 2: DFX versus DFO, Outcome 2: SAEs (thalassaemia)

Study or Subgroup	DFX Events	DFX Total	DFO Events	DFO Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Total thalassaemia-related SAEs						
Hassan 2016	0	30	0	30		Not estimable
Pennell 2014	10	96	10	91	100.0%	0.95 [0.41 , 2.17]
Subtotal (95% CI)		**126**		**121**	**100.0%**	**0.95 [0.41 , 2.17]**
Total events:	10		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						

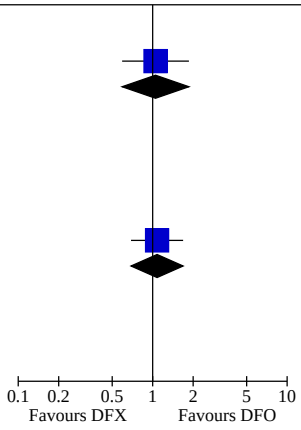


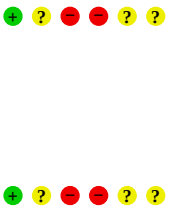


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 2.3. Comparison 2: DFX versus DFO, Outcome 3: SAEs (sickle cell disease)

Study or Subgroup	DFX Events	DFX Total	DFO Events	DFO Total	Weight	Risk Ratio M-H, Random, 99% CI
2.3.1 Painful crisis						
Vichinsky 2007	44	132	20	63	100.0%	1.05 [0.59 , 1.86]
Subtotal (99% CI)		**132**		**63**	**100.0%**	**1.05 [0.59 , 1.86]**
Total events:	44		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.22 (P = 0.83)						
2.3.2 Other sickle cell disease-related SAEs						
Vichinsky 2007	61	132	27	63	100.0%	1.08 [0.69 , 1.68]
Subtotal (99% CI)		**132**		**63**	**100.0%**	**1.08 [0.69 , 1.68]**
Total events:	61		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						



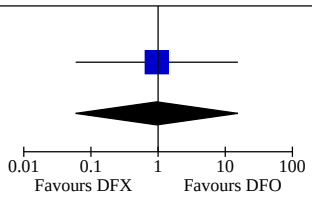


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 2.4. Comparison 2: DFX versus DFO, Outcome 4: All-cause mortality (thalassaemia)

Study or Subgroup	DFX Events	DFX Total	DFO Events	DFO Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hassan 2016	0	30	0	30		Not estimable
Pennell 2014	1	92	1	88	100.0%	0.96 [0.06 , 15.42]
Total (95% CI)		**122**		**118**	**100.0%**	**0.96 [0.06 , 15.42]**
Total events:	1		1			

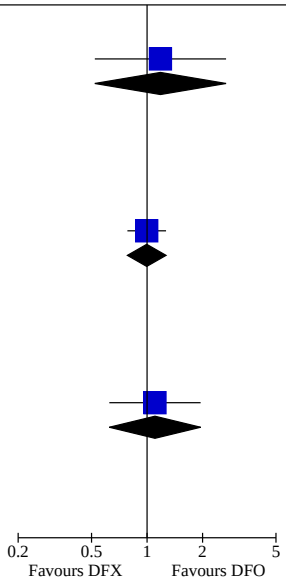
Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.97)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias): All outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.5. Comparison 2: DFX versus DFO, Outcome 5: Proportion of participants with iron overload (thalassaemia)

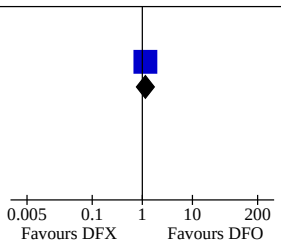
Study or Subgroup	DFX Events	DFX Total	DFO Events	DFO Total	Weight	Risk Ratio M-H, Random, 99% CI
2.5.1 Iron overload defined by ferritin 1500 (µg/l) or higher (thalassaemia)						
Hassan 2016	13	30	11	30	100.0%	1.18 [0.52 , 2.68]
Subtotal (99% CI)		**30**		**30**	**100.0%**	**1.18 [0.52 , 2.68]**
Total events:	13		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						
2.5.2 Proportion with severe iron overload (liver iron concentration at least 15 mg/Fe/g dry weight)						
Pennell 2014	66	91	59	81	100.0%	1.00 [0.78 , 1.27]
Subtotal (99% CI)		**91**		**81**	**100.0%**	**1.00 [0.78 , 1.27]**
Total events:	66		59			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
2.5.3 Myocardial T2* < 10 ms						
Pennell 2014	31	91	25	81	100.0%	1.10 [0.62 , 1.95]
Subtotal (99% CI)		**91**		**81**	**100.0%**	**1.10 [0.62 , 1.95]**
Total events:	31		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.66)						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 2.6. Comparison 2: DFX versus DFO, Outcome 6: Total AEs related to iron chelation - (thalassaemia)

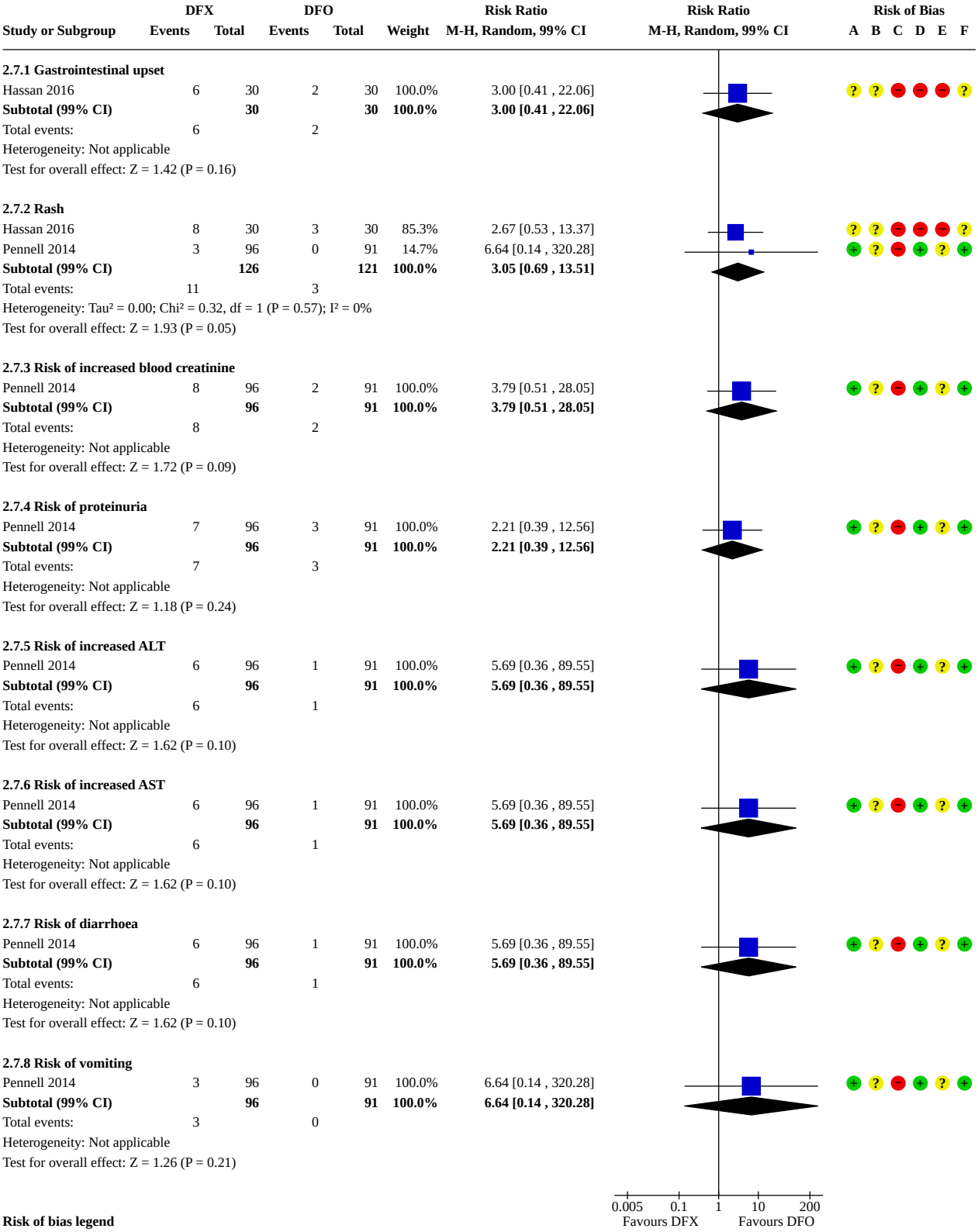
Study or Subgroup	DFX Events	DFX Total	DFO Events	DFO Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
2.6.1 Total chelation-related AEs							
Pennell 2014	34	96	28	91	100.0%	1.15 [0.76 , 1.73]	+ ? − + ? ? +
Subtotal (95% CI)		**96**		**91**	**100.0%**	**1.15 [0.76 , 1.73]**	
Total events:	34		28				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.67 (P = 0.50)							



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias): All outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.7. Comparison 2: DFX versus DFO, Outcome 7: Other AEs related to iron chelation - (thalassaemia)



Risk of bias legend

(A) Random sequence generation (selection bias)

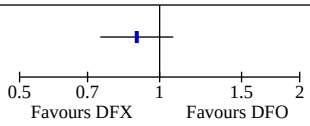
(B) Allocation concealment (selection bias)

Analysis 2.7. (Continued)

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

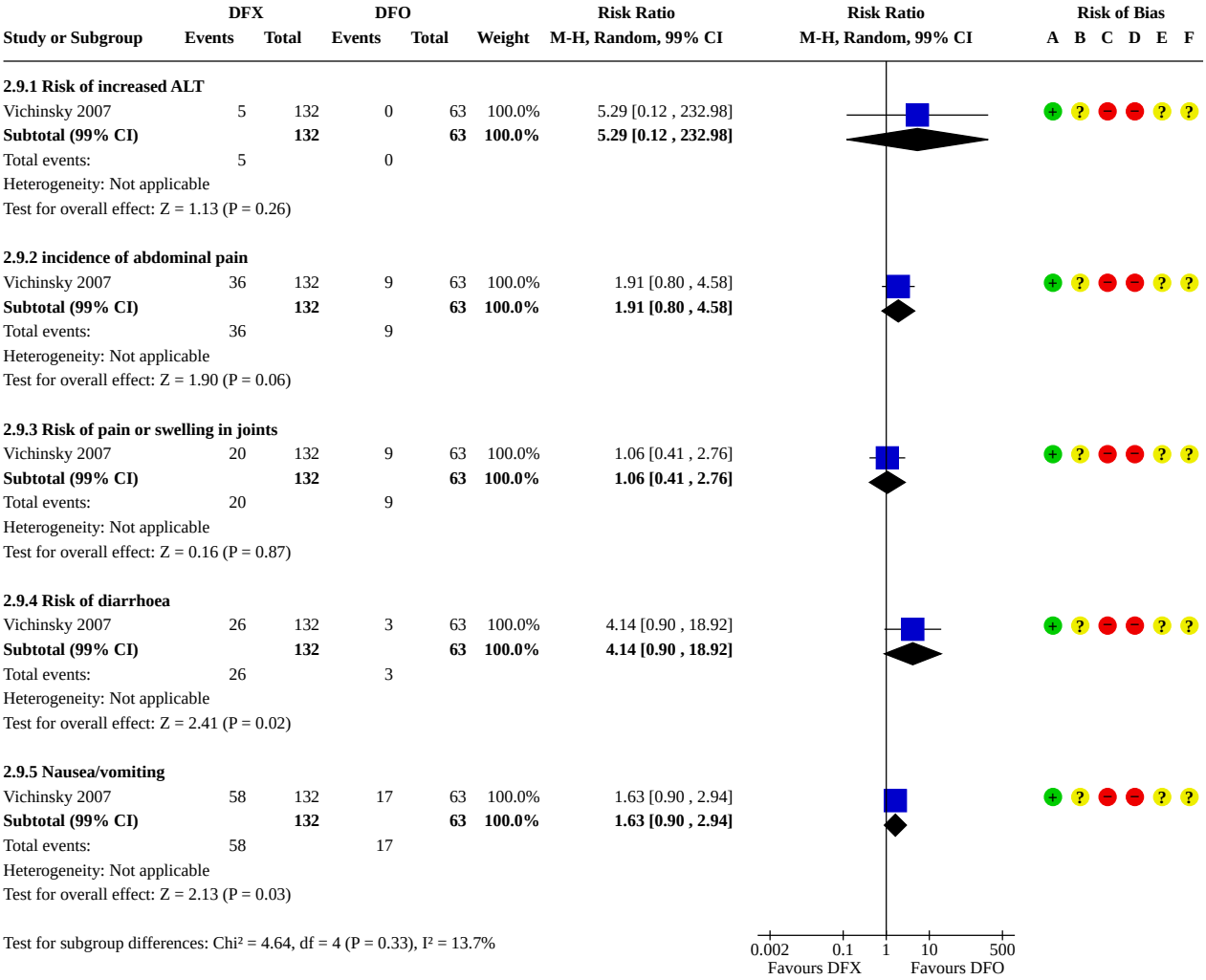
Analysis 2.8. Comparison 2: DFX versus DFO, Outcome 8: Total AEs (thalassaemia)

Study or Subgroup	DFX Events	DFX Total	DFO Events	DFO Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Pennell 2014	65	96	69	91	0.89 [0.75 , 1.07]		+ ? − + ? ? +



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias): All outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.9. Comparison 2: DFX versus DFO, Outcome 9: Other AEs related to iron chelation (SCD)



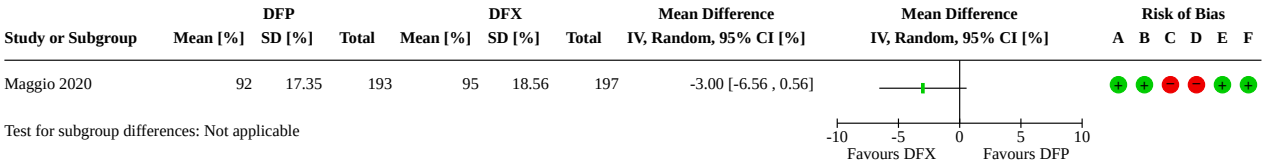
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Comparison 3. DFP versus DFX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Adherence to iron chelation (%, SD)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.2 Total SAEs	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.2.1 12 months	1	390	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.46, 1.96]
3.3 SAE (chelation-related) (n/N)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3.1 12 months	1	390	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.54 [0.44, 5.39]
3.4 All-cause mortality (n/N)	1		Risk Difference (M-H, Random, 95% CI)	Subtotals only
3.4.1 12 months	1	390	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]

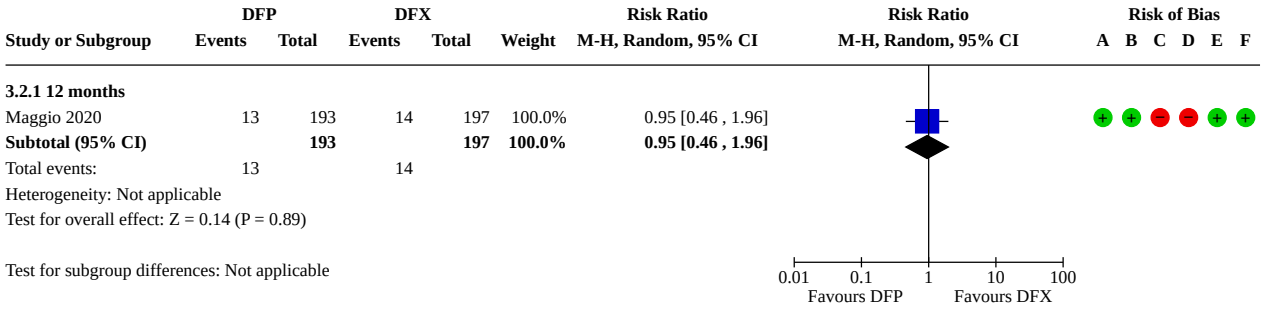
Analysis 3.1. Comparison 3: DFP versus DFX, Outcome 1: Adherence to iron chelation (%, SD)



Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 3.2. Comparison 3: DFP versus DFX, Outcome 2: Total SAEs

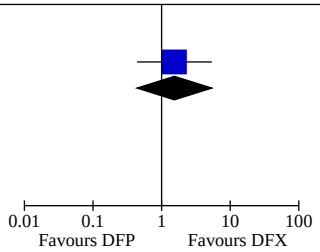


Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 3.3. Comparison 3: DFP versus DFX, Outcome 3: SAE (chelation-related) (n/N)

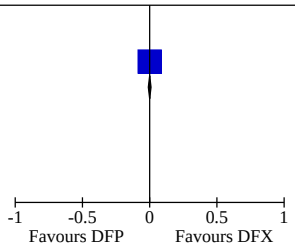
Study or Subgroup	DFP Events	DFP Total	DFX Events	DFX Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F
3.3.1 12 months							
Maggio 2020	6	193	4	197	100.0%	1.54 [0.44 , 5.39]	+ + − − + +
Subtotal (95% CI)		**193**		**197**	**100.0%**	**1.54 [0.44 , 5.39]**	
Total events:	6		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.67 (P = 0.50)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 3.4. Comparison 3: DFP versus DFX, Outcome 4: All-cause mortality (n/N)

Study or Subgroup	DFP Events	DFP Total	DFX Events	DFX Total	Weight	Risk Difference M-H, Random, 95% CI	Risk of Bias A B C D E F
3.4.1 12 months							
Maggio 2020	0	193	0	197	100.0%	0.00 [-0.01 , 0.01]	+ + − − + +
Subtotal (95% CI)		**193**		**197**	**100.0%**	**0.00 [-0.01 , 0.01]**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.00 (P = 1.00)							
Test for subgroup differences: Not applicable							



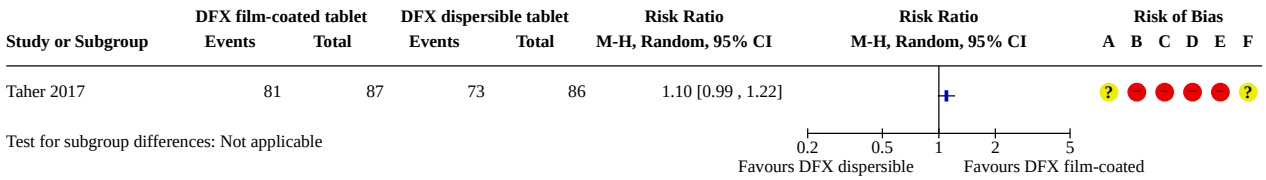
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Comparison 4. DFX film-coated tablet versus DFX dispersible tablet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Adherence to iron chelation therapy (n/N)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.2 Adherence to iron chelation therapy (%, SD)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.2.1 13 weeks	1	91	Mean Difference (IV, Random, 95% CI)	5.00 [-6.75, 16.75]
4.2.2 24 weeks	1	54	Mean Difference (IV, Random, 95% CI)	7.00 [-8.94, 22.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3 Incidence of SAEs	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.4 All-cause mortality	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.5 Incidence of organ damage	1	173	Risk Ratio (M-H, Random, 99% CI)	1.25 [0.72, 2.18]
4.5.1 Renal events	1	173	Risk Ratio (M-H, Random, 99% CI)	1.25 [0.72, 2.18]
4.6 Total AEs related to iron chelation	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.6.1 Total chelation-related AEs	1	173	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.57, 0.99]
4.7 Other AEs related to iron chelation	1		Risk Ratio (M-H, Random, 99% CI)	Subtotals only
4.7.1 Risk of diarrhoea	1	173	Risk Ratio (M-H, Random, 99% CI)	0.70 [0.29, 1.70]
4.7.2 Increased urine protein/urine creatinine ratio	1	173	Risk Ratio (M-H, Random, 99% CI)	1.65 [0.60, 4.54]
4.7.3 incidence of abdominal pain	1	173	Risk Ratio (M-H, Random, 99% CI)	0.49 [0.16, 1.52]
4.7.4 Incidence of nausea	1	173	Risk Ratio (M-H, Random, 99% CI)	0.72 [0.23, 2.23]
4.7.5 Incidence of vomiting	1	173	Risk Ratio (M-H, Random, 99% CI)	0.28 [0.07, 1.15]

Analysis 4.1. Comparison 4: DFX film-coated tablet versus DFX dispersible tablet, Outcome 1: Adherence to iron chelation therapy (n/N)

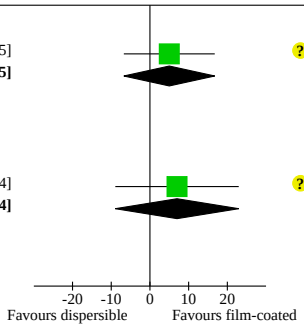


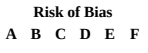
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 4.2. Comparison 4: DFX film-coated tablet versus DFX dispersible tablet, Outcome 2: Adherence to iron chelation therapy (%, SD)

Study or Subgroup	DFX film-coated Mean [%]	SD [%]	Total	DFX dispersible tablet Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Random, 95% CI [%]
4.2.1 13 weeks								
Taher 2017	89.3	22.63	41	84.3	34.22	50	100.0%	5.00 [-6.75 , 16.75]
Subtotal (95% CI)			**41**			**50**	**100.0%**	**5.00 [-6.75 , 16.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.83 (P = 0.40)								
4.2.2 24 weeks								
Taher 2017	89.9	25.47	24	82.9	34.26	30	100.0%	7.00 [-8.94 , 22.94]
Subtotal (95% CI)			**24**			**30**	**100.0%**	**7.00 [-8.94 , 22.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.86 (P = 0.39)								

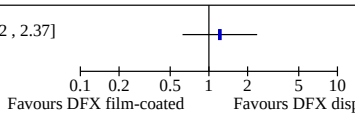


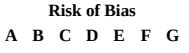


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 4.3. Comparison 4: DFX film-coated tablet versus DFX dispersible tablet, Outcome 3: Incidence of SAEs

Study or Subgroup	DFX film-coated tablet Events	Total	DFX dispersible tablet Events	Total	Risk Ratio M-H, Random, 95% CI
Taher 2017	16	87	13	86	1.22 [0.62 , 2.37]
Test for subgroup differences: Not applicable					

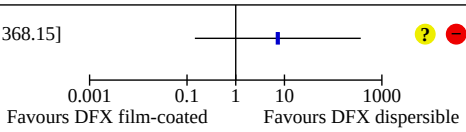


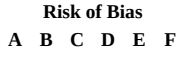


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias): All outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.4. Comparison 4: DFX film-coated tablet versus DFX dispersible tablet, Outcome 4: All-cause mortality

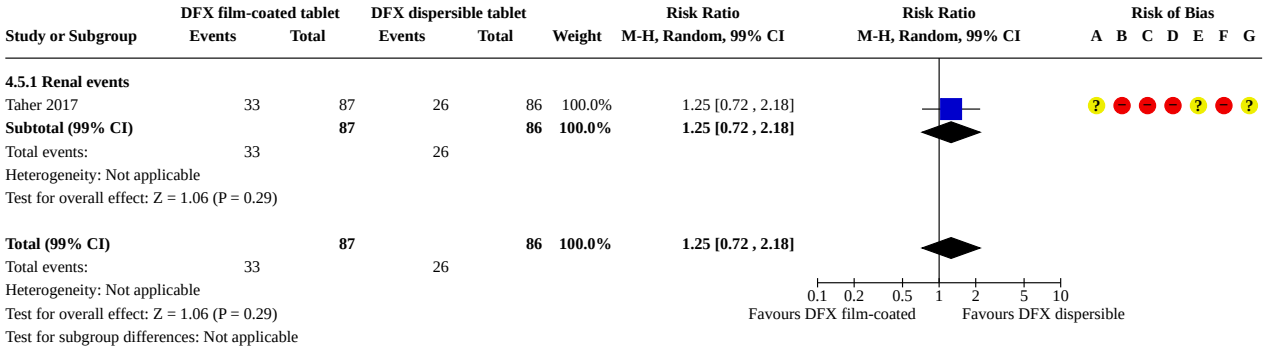
Study or Subgroup	DFX FCT Events	Total	DFX DT Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Taher 2017	1	87	0	86	7.30 [0.14 , 368.15]
Test for subgroup differences: Not applicable					





Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

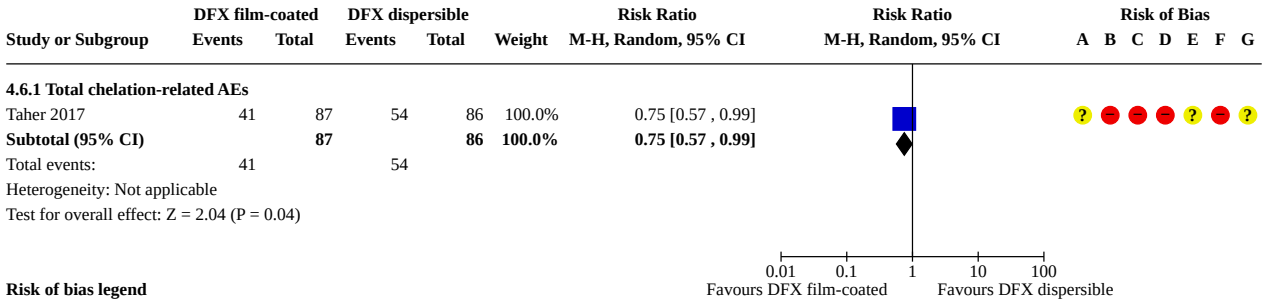
Analysis 4.5. Comparison 4: DFX film-coated tablet versus DFX dispersible tablet, Outcome 5: Incidence of organ damage



Study or Subgroup	DFX film-coated tablet Events	Total	DFX dispersible tablet Events	Total	Weight	Risk Ratio M-H, Random, 99% CI
4.5.1 Renal events						
Taher 2017	33	87	26	86	100.0%	1.25 [0.72 , 2.18]
Subtotal (99% CI)		**87**		**86**	**100.0%**	**1.25 [0.72 , 2.18]**
Total events:	33		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Total (99% CI)		**87**		**86**	**100.0%**	**1.25 [0.72 , 2.18]**
Total events:	33		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Test for subgroup differences: Not applicable						

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias): All outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

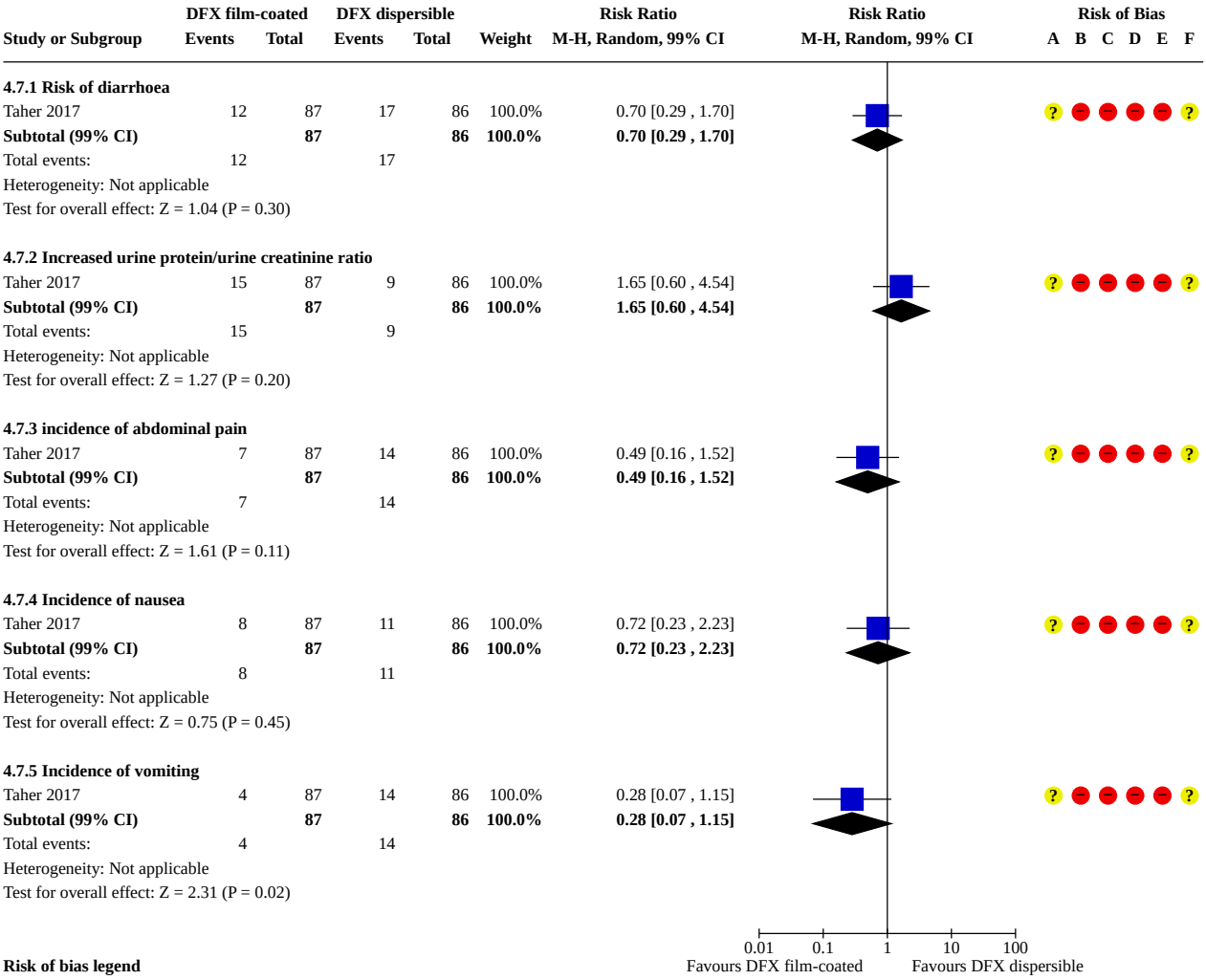
Analysis 4.6. Comparison 4: DFX film-coated tablet versus DFX dispersible tablet, Outcome 6: Total AEs related to iron chelation



Study or Subgroup	DFX film-coated Events	Total	DFX dispersible Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.6.1 Total chelation-related AEs						
Taher 2017	41	87	54	86	100.0%	0.75 [0.57 , 0.99]
Subtotal (95% CI)		**87**		**86**	**100.0%**	**0.75 [0.57 , 0.99]**
Total events:	41		54			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.04 (P = 0.04)						

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias): All outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.7. Comparison 4: DFX film-coated tablet versus DFX dispersible tablet, Outcome 7: Other AEs related to iron chelation



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Comparison 5. DFP and DFO versus DFP

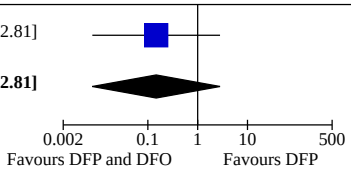
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Incidence of SAEs	1	213	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.01, 2.81]
5.2 All-cause mortality	2	237	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.77 [0.17, 3.42]
5.3 Incidence of chelation therapy-related AEs	3		Risk Ratio (M-H, Random, 99% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3.1 Risk of leukopenia, neutropenia and/or agranulocytosis	3	280	Risk Ratio (M-H, Random, 99% CI)	1.15 [0.50, 2.62]
5.3.2 Risk of pain or swelling in joints	2	256	Risk Ratio (M-H, Random, 99% CI)	0.76 [0.31, 1.91]
5.3.3 Risk of gastrointestinal disturbances	1	213	Risk Ratio (M-H, Random, 99% CI)	0.45 [0.15, 1.37]
5.3.4 Risk of increased liver transaminase	2	256	Risk Ratio (M-H, Random, 99% CI)	1.02 [0.52, 1.98]
5.3.5 Nausea/vomiting	1	43	Risk Ratio (M-H, Random, 99% CI)	0.55 [0.13, 2.23]

Analysis 5.1. Comparison 5: DFP and DFO versus DFP, Outcome 1: Incidence of SAEs

Study or Subgroup	DFP and DFO Events	DFP and DFO Total	DFP Events	DFP Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Maggio 2009	0	105	3	108	100.0%	0.15 [0.01 , 2.81]	+ + − + + ?
Total (95% CI)		**105**		**108**	**100.0%**	**0.15 [0.01 , 2.81]**	
Total events:	0		3				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.27 (P = 0.20)
Test for subgroup differences: Not applicable

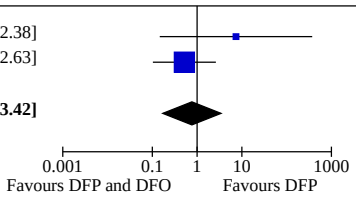


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 5.2. Comparison 5: DFP and DFO versus DFP, Outcome 2: All-cause mortality

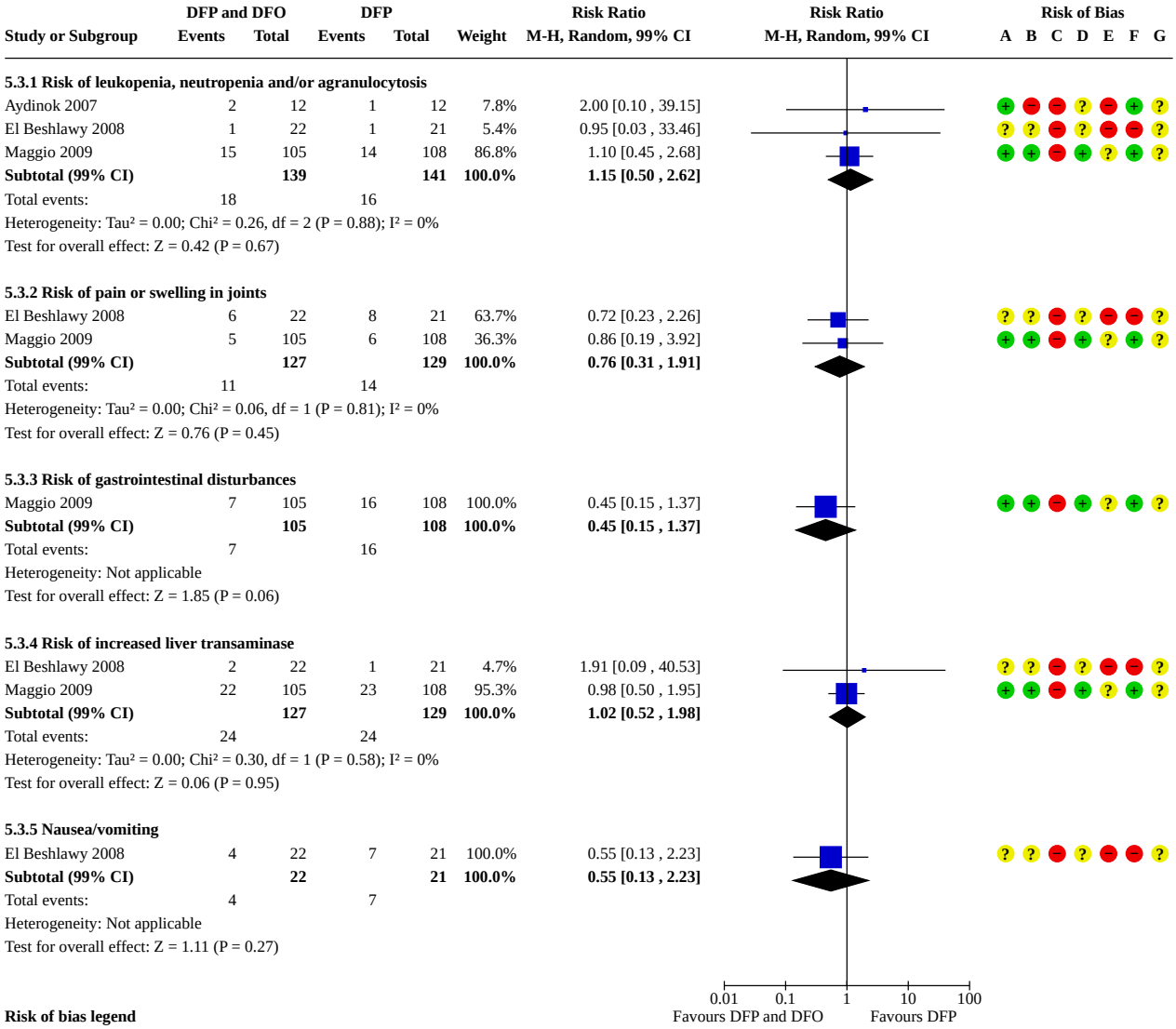
Study or Subgroup	DFP and DFO Events	DFP and DFO Total	DFP Events	DFP Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F G
Aydinok 2007	1	12	0	12	14.6%	7.39 [0.15 , 372.38]	+ − − ? − + ?
Maggio 2009	2	105	4	108	85.4%	0.52 [0.10 , 2.63]	+ + − + ? + ?
Total (95% CI)		**117**		**120**	**100.0%**	**0.77 [0.17 , 3.42]**	
Total events:	3		4				

Heterogeneity: Chi² = 1.50, df = 1 (P = 0.22); I² = 34%
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias): All outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.3. Comparison 5: DFP and DFO versus DFP, Outcome 3: Incidence of chelation therapy-related AEs



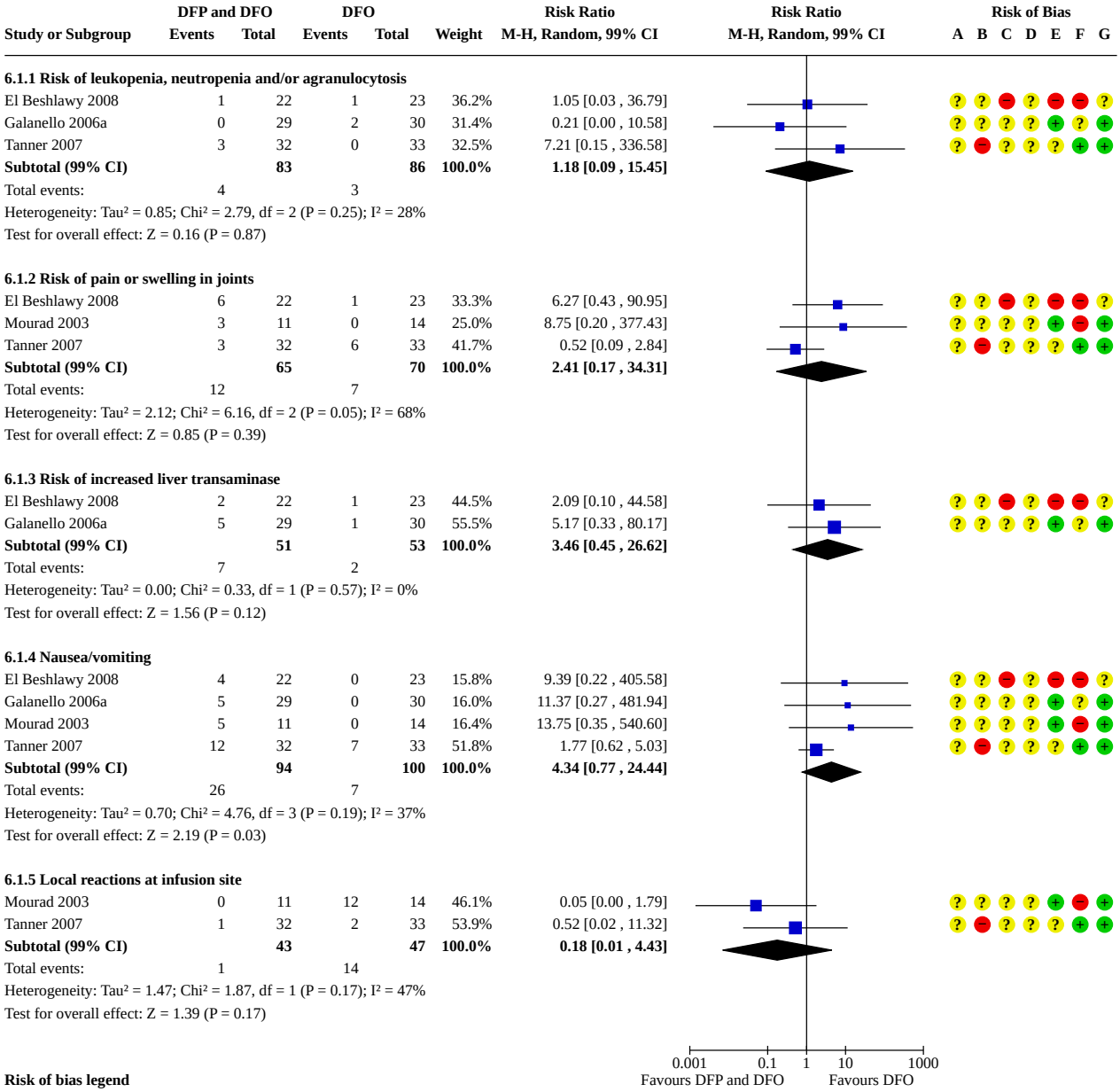
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias): All outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 6. DFP and DFO versus DFO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Other AEs related to iron chelation	4		Risk Ratio (M-H, Random, 99% CI)	Subtotals only
6.1.1 Risk of leukopenia, neutropenia and/or agranulocytosis	3	169	Risk Ratio (M-H, Random, 99% CI)	1.18 [0.09, 15.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1.2 Risk of pain or swelling in joints	3	135	Risk Ratio (M-H, Random, 99% CI)	2.41 [0.17, 34.31]
6.1.3 Risk of increased liver transaminase	2	104	Risk Ratio (M-H, Random, 99% CI)	3.46 [0.45, 26.62]
6.1.4 Nausea/vomiting	4	194	Risk Ratio (M-H, Random, 99% CI)	4.34 [0.77, 24.44]
6.1.5 Local reactions at infusion site	2	90	Risk Ratio (M-H, Random, 99% CI)	0.18 [0.01, 4.43]

Analysis 6.1. Comparison 6: DFP and DFO versus DFO, Outcome 1: Other AEs related to iron chelation



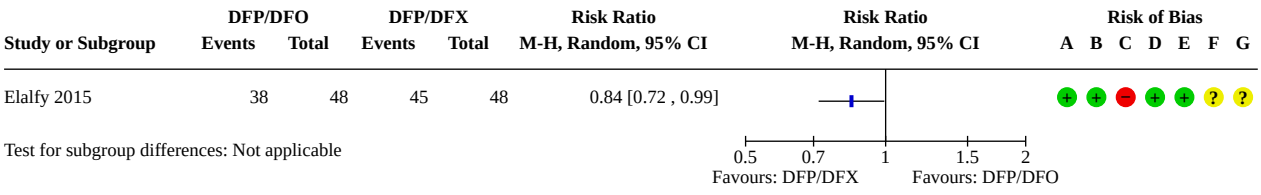
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias): All outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 7. DFP and DFX versus DFP and DFO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Adherence to iron chelation therapy rates	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 Incidence of SAE	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.3 All-cause mortality	1		Risk Difference (M-H, Random, 95% CI)	Totals not selected
7.4 Organ damage (serum creatinine (≥ 33%) above baseline on 2 consecutive occasions)	1		Risk Ratio (M-H, Random, 99% CI)	Subtotals only
7.5 Total AEs related to iron chelation	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.5.1 one year (study end)	1	96	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.76, 1.53]
7.6 Other AEs related to iron chelation	1		Risk Ratio (M-H, Random, 99% CI)	Subtotals only
7.6.1 Risk of leukopenia, neutropenia and/or agranulocytosis	1	96	Risk Ratio (M-H, Random, 99% CI)	1.67 [0.27, 10.14]
7.6.2 Risk of pain or swelling in joints	1	96	Risk Ratio (M-H, Random, 99% CI)	0.89 [0.29, 2.77]
7.6.3 Gastrointestinal problems	1	96	Risk Ratio (M-H, Random, 99% CI)	0.60 [0.18, 2.04]
7.6.4 ALT (increase ≥ 3-fold)	1	96	Risk Ratio (M-H, Random, 99% CI)	1.33 [0.20, 8.88]
7.6.5 Skin rash	1	96	Risk Ratio (M-H, Random, 99% CI)	5.00 [0.10, 261.34]

Analysis 7.1. Comparison 7: DFP and DFX versus DFP and DFO, Outcome 1: Adherence to iron chelation therapy rates

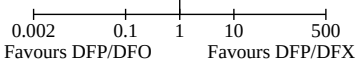


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias): All outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.2. Comparison 7: DFP and DFX versus DFP and DFO, Outcome 2: Incidence of SAE

Study or Subgroup	DFP/DFO Events	DFP/DFO Total	DFP/DFX Events	DFP/DFX Total	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F
Elalfy 2015	1	48	1	48	1.00 [0.06 , 16.22]		+ + − + ? ?

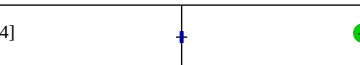
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 7.3. Comparison 7: DFP and DFX versus DFP and DFO, Outcome 3: All-cause mortality

Study or Subgroup	DFP/DFO Events	DFP/DFO Total	DFP/DFX Events	DFP/DFX Total	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% CI	Risk of Bias A B C D E F G
Elalfy 2015	0	48	0	48	0.00 [-0.04 , 0.04]		+ + − + + ? ?

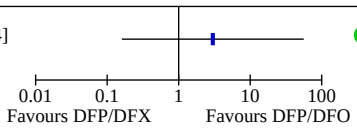


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias): All outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.4. Comparison 7: DFP and DFX versus DFP and DFO, Outcome 4: Organ damage (serum creatinine (≥ 33%) above baseline on 2 consecutive occasions)

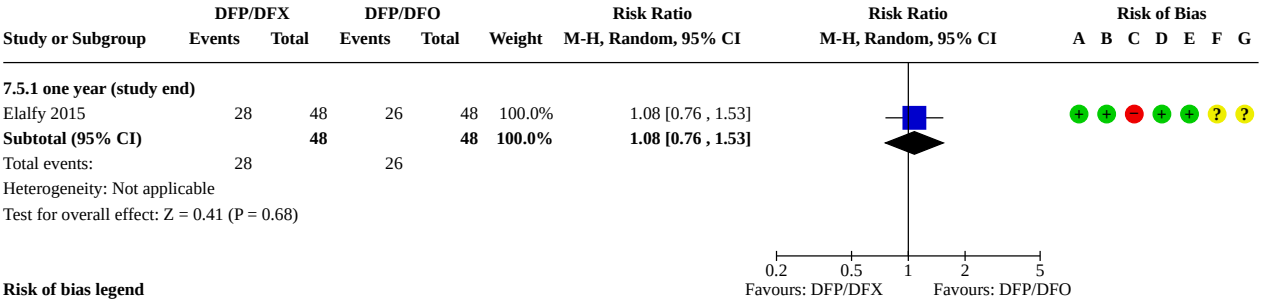
Study or Subgroup	DFP/DFX Events	DFP/DFX Total	DFP/DFO Events	DFP/DFO Total	Risk Ratio M-H, Random, 99% CI	Risk Ratio M-H, Random, 99% CI	Risk of Bias A B C D E F
Elalfy 2015	3	48	1	48	3.00 [0.16 , 56.04]		+ + − + ? ?

Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

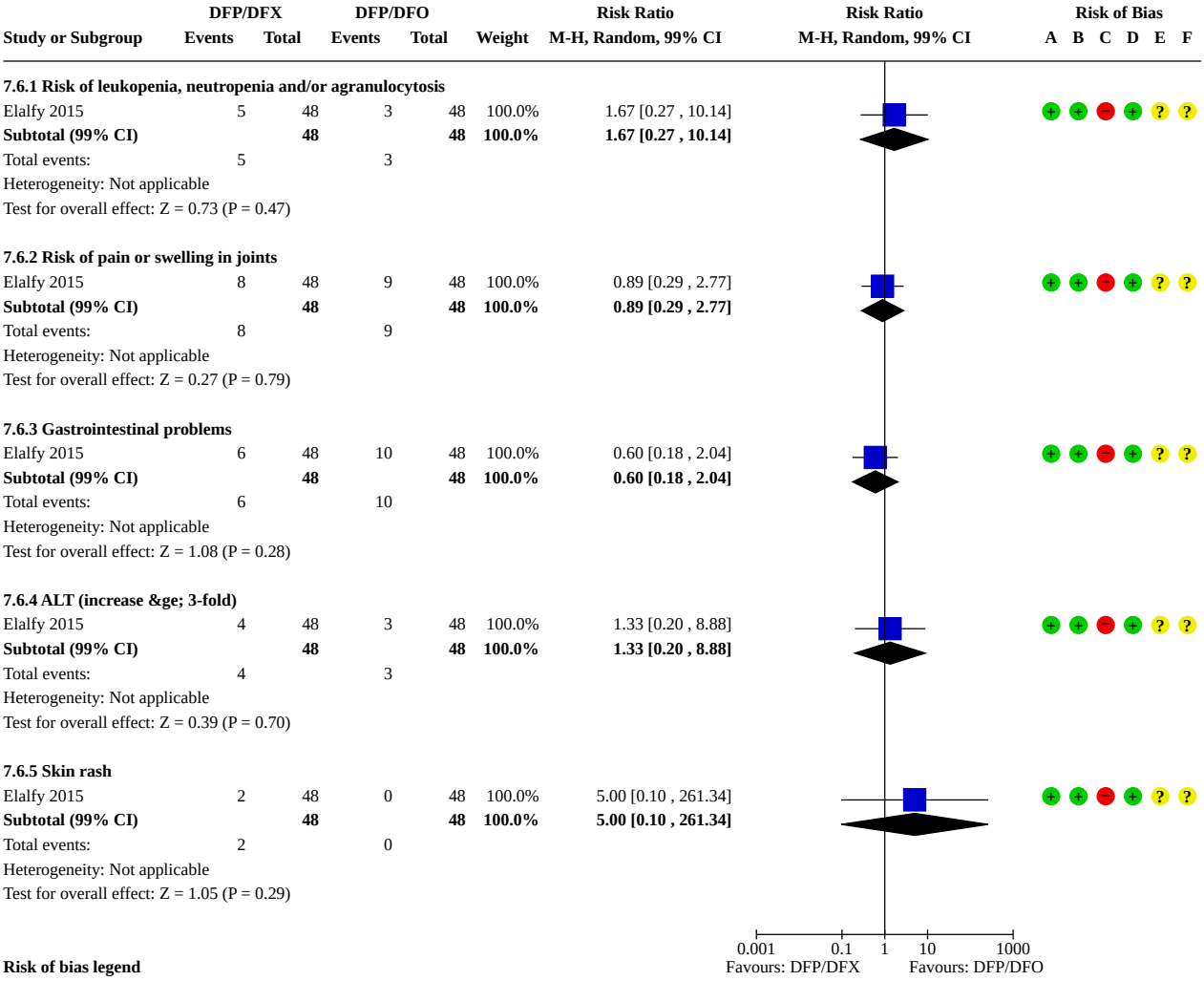
Analysis 7.5. Comparison 7: DFP and DFX versus DFP and DFO, Outcome 5: Total AEs related to iron chelation



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias): All outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.6. Comparison 7: DFP and DFX versus DFP and DFO, Outcome 6: Other AEs related to iron chelation



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Selective reporting (reporting bias)
(F) Other bias

ADDITIONAL TABLES

Table 1. Adherence measurement and results table

Study	How adherence was measured	Results
Aydinok 2007	Drug accounting at each visit (by counting the returned empty blisters of DFP and used vials of DFO)	Compliance was generally excellent during the entire trial period
	Trial-specific designed questionnaire completed by the participants or their legal representative/guardian (or both) at quarterly intervals	1 participant in the DFP treatment arm who missed more than 1 chelation dose/week because of problems with swallowing

Table 1. Adherence measurement and results table *(Continued)*

Badawy 2010	Questionnaire on chelation therapy, reasons for non-compliance, side effects, life activities, transfusion regimen	Combined therapy, and DFP only groups were more compliant (than DFO only) to chelation therapy, but difference was statistically non-significant Non-compliant participants (compliance less than 50%) showed increase in their SF levels in all studied groups In non-compliant participants the reduction in SF levels was higher in group I and III than in group II, but difference was statistically non-significant
Bahnasawy 2017	Clinical pharmacist analysed data to detect unnecessary drug therapy, need for additional drug therapy, ineffective drug product, dosage too low, adverse drug reaction, dosage too high, non-compliance	All 24 participants in intervention group had non-adherence at baseline and 3 were non-adherent at end of trial No data on control group
Calvaruso 2014	Counting the number of DFP pills in each returned bag Assessing the number of infusions of DFO registered on the electronic pump	DFP compliance rate: 89% DFO compliance rate: 75% No information regarding N or time point measured
Calvaruso 2015	Counting the number of DFP pills in each returned bag Assessing the number of infusions of DFO registered on the electronic pump	DFP compliance rate: 85% DFO compliance rate: 76% No information regarding N or time point measured
El Beshlawy 2008	Counting the returned empty blisters of DFP Counting used vials of DFO	4 participants with DFO-based regimen excluded from the trial due to lack of compliance Compliance was otherwise excellent during the entire trial period Majority of participants had no problems with the intake and swallowing of the DFP tablets

Table 1. Adherence measurement and results table *(Continued)*

		80% of participants in the combination arm and 76% of participants in the DFO monotherapy arm complained about difficulties in the parenteral use of DFO or problems to insert a needle
Elalfy 2015	Counting of returned tablets for the oral chelators	DFP/DFX: 95%
	Counting vials for DFO	DFP/DFO: 80%
	The percentage of actual dose that the participant had taken in relation to the total prescribed dose was calculated	
Galanello 2006	DFP assessed by pill counts, diary cards and an electronic cap that recorded the time and date of each opening of the tablet container	DFP/DFO: DFO: 96.1 ± 5.0 (29 participants)
		DFP compliance was not reported
	DFO assessed by diary cards, weekly physical examination of infusion sites, and by the Crono™ infusion pump that recorded the number of completed infusions	DFO: 95.7 ± 5.7 (30 participants)
Gharaati 2019	Questionnaire developed by researchers in 4 sections: 1. Background: type of chelation drugs taken, frequency of taking chelation drugs on a weekly basis, frequency of injections on a monthly basis 2. Patient knowledge of medications and self-care behaviour 3. Attitude to status, medication and self-care 4. Showing self-care behaviours	"phone-mediated education managed to improve the use of chelation drugs in the intervention group and regulate patients' visits to hospital for blood injection" However, baseline difference may have biased this
Hassan 2016	Records of all trial medications that were dispensed and returned	All participants compliant with prescribed doses
	Parents were instructed to contact the investigator if the participants were unable to take the trial drug as prescribed	No discontinuation of drugs or dropout of follow-up occurred
Kwiatkowsi 2021	Treatment compliance was measured monthly by counting the number of tablets or measuring the volume of oral solution returned for participants on deferiprone, and by checking the infusion pump electronic record for participants on deferoxamine	Treatment compliance throughout the study was similar between the groups (P = 0.12)
		DFP: 68.9%
	In addition, participants were asked to record their medication usage in a diary	DFO: 78.9%

Table 1. Adherence measurement and results table *(Continued)*

	Participants who took 80% to 120% of the prescribed dose were considered to be compliant	
Maggio 2009	Counting the pills in each returned bag of DFP Assessing the number of infusions of DFO registered on the electronic pump	DFP–DFO group, mean (SD; range): DFP 92.7% (15.2%; 37% to 100%); DFO 70.6% (24.1%; 25% to 100%) DFP alone group, mean (SD; range): 93.6% (9.7%; 56% to 100%)
Maggio 2020	Compliance was appropriate if the proportion of prescribed therapy taken was at least 80% Compliance was estimated from electronic case report form data and the proportion of the prescribed doses taken	Appropriate compliance: DFP, proportion, mean (SD), median (IQR): 183/193 (95%) participants, mean 92% (17.35), 93% (13.6) DFX, proportion, mean (SD), median (IQR): 192/197 (97%) participants, 95% (18.56), 97% (11.1)
Mourad 2003	Number of vials of DFX used Number of tablets of DFO used	DFO/DFX group: compliance was excellent (arbitrarily defined as taking > 90% of the recommended doses) in 10 participants and good (75% to 90% of recommended doses) in 1 participant DFX alone group: compliance was considered to be excellent in 11 participants and good in 3 participants
Olivieri 1997	% of doses administered: number of doses of the iron chelator taken, out of number prescribed DFP measured with computerised bottles DFO measured using ambulatory pumps Measured for a minimum of 3 months	DFP, mean (SD): 94.9% (1.1%) DFO, mean (SD): 71.6% (3.7%)
Pennell 2006	DFP: measured using the Medication Event Monitoring System device calculated as the percent of openings with an interval longer than 4 hours recorded, divided by number of doses prescribed DFO: calculated as the percentage of completed infusions, as determined by the Crono pumps, divided by the number of infusions prescribed	DFP, mean (SD): 94% (5.3%) DFO, mean (SD): 93% (9.7%)
Pennell 2014	Not stated how adherence was measured	DFX, mean (SD): 99.0% (3.5%)

Table 1. Adherence measurement and results table *(Continued)*

		DFO, mean (SD): 100.4% (10.9%)
Taher 2017	Assessed by relative consumed tablet count	DT: 85.3% (95% CI 81.1 to 89.5) FCT: 92.9% (95% CI 88.8 to 97.0) Also reported as n/N, unrelated to % (SD) reported above: DT: 73/86 (84.9%) FCT: 81/87 (93.1%) FCT vs DT: RR 1.10 (95%CI 0.99, 1.22)
Tanner 2007	DFO: calculated as the percentage of completed infusions, as determined by the Crono pumps, divided by the number of infusions prescribed	DFO/placebo, mean (SD): DFO 91.4% (2.7%); placebo 89.8 (7.2%)
	DFP/placebo: pill counting at the bi-monthly visits	DFO/DFP, mean (SD): DFO 92.6 (2.7%); DFP: 82.4% (18.1%)
Vichinsky 2007	DFX: counting the number of tablets returned in bottles at each visit	Ratios of the administered to intended doses of therapy were high (1.16 for DFX and 0.97 for DFO), indicating high adherence to the prescribed treatment regimens
	DFO: counting the numbers of vials returned at each visit	

DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; DT: dispersible tablet; FCT: film-coated tablet; IQR: interquartile range; RR: risk ratio; SD: standard deviation; SF: serum ferritin

Table 2. Study overview: Comparison 1. DFP versus DFO

Study	Participants	Intervention	Comparator	Outcomes
Badawy 2010*	Age > 8 years	DFP	DFO	Adherence
Egypt	β-thalassaemia (100%)	75 mg/kg/day, daily	40 mg/kg/day, 5 days/week	AEs
		n = 50	n = 50	
Calvaruso 2014	Age > 13 years	DFP	DFO	Compliance
Italy	SCD (100%)	75 mg/kg/day, divided into 3 oral daily doses (daily)	SC infusion (8 to 10 hours) at 50 mg/kg/day for 5 days/week	Mortality (5 years) AEs (not SAEs)
		n = 30	n = 30	
Calvaruso 2015	Age > 13 years	DFP	DFO	Adherence
Italy	Thalassaemia intermedia (100%)	75 mg/kg/day, divided into 3 oral daily doses (daily)	SC infusion (8 to 10 hours) at 50 mg/kg/day for 5 days/week	Compliance Mortality (5 years)
		n = 47	n = 41	

Table 2. Study overview: Comparison 1. DFP versus DFO *(Continued)*

El Beshlawy 2008 Egypt	Age > 4 years β-thalassaemia (100%)	DFP 60 to 83 mg/kg/day (daily) n = 18	DFO 23 to 50 mg kg/day for 5 days/week n = 20	Adherence Compliance AEs Iron overload
Kwiatkowski 2021 USA Note: terminated early	Age > 2 years SCD or other iron overload (excluded thalassaemia or MDS)	DFP 75 mg/kg (25 mg/kg per dose); 3/day, 8 hours apart to 99 mg/kg for more severe n = 152	DFO SC infusion (8 to 12 hours) 20 to 40 mg/kg/day for 5 to 7 days/week n = 76	12 months: Adherence Mortality HRQoL SAEs (chelation associated) All SAEs Other AEs related to chelation
Olivieri 1997 Canada	Age > 10 years β-thalassaemia major (100%)	DFP 75 mg/kg/day in 3 divided doses n = 19	DFO 50 mg/kg/night, 4 to 7 nights/week n = 18	Adherence (3 months)
Pennell 2006 Italy and Greece	Age > 18 years β-thalassaemia major (100%)	DFP 75 mg/kg/day increasing to 100 mg/kg/day. Mean actual dose: 92 mg/kg/day n = 29	DFO SC injection 50 mg/kg for 5 or more days/week n = 32	Adherence AEs

*Badawy 2010 did not report any outcomes by intervention group and did not include counts of events (i.e. AEs) and so was not included in the quantitative analysis.
Badawy 2010 and El Beshlawy 2008 are 3-arm trials (DFP, DFO vs DFP vs DFO) and so are listed in more than one comparison.
AE: adverse events; DFO: deferoxamine; DFP: deferiprone; MDS: myelodysplastic syndromes; SAE: serious adverse events; SC: subcutaneous; SCD: sickle cell disease; SF: serum ferritin

Table 3. Study overview: Comparison 2. DFX versus DFO

Study	Participants	Intervention	Comparator	Outcomes
Hassan 2016 Egypt	Age > 6 years β-thalassaemia major	DFX 20 to 40 mg/kg/day on an empty stomach n = 30	DFO 20 to 50 mg/kg/day via SC infusion over 8 to 10 hours, 5 days/week n = 30	Adherence Drug safety
Pennell 2014 CORDELIA (multi-national: 11 countries)	Age > 10 years β-thalassaemia (100%)	DFX 20 mg/kg per day for 2 weeks, then 30 mg/kg/day for 1 week,	DFO 50 to 60 mg/kg/day via SC infusion over 8 to 12 hours, 5 to 7 days/week	1 year: Adherence LIC

Table 3. Study overview: Comparison 2. DFX versus DFO *(Continued)*

		then 40 mg/kg/day n = 98	n = 99	SF
Vichinsky 2007 (Multi-national: 5 countries)	Age > 2 years SCD	DFX 10 to 30 mg/kg according to baseline LIC (daily) n = 132	DFO 50 to 70 mg/kg slow SC infusion over 8 to 12 hours, 5 to 7 days/week n = 63	52 weeks: Adherence Safety LIC SF

DFO: deferoxamine; DFX: deferasirox; LIC: liver iron content; SC: subcutaneous; SCD: sickle cell disease, SF: serum ferritin

Table 4. Study overview: Comparison 3. DFP versus DFX

Study	Participants	Intervention	Comparator	Outcomes
Maggio 2020 DEEP-2 (multi-national)	Age 1 month to 18 years Any hereditary haemoglobinopathy: including thalassaemia and SCD	DFP 75 to 100 mg/kg/day, orally, daily n = 193	DFX (dispersible tablets) 20 to 40 mg/kg/day n = 197	12 months: Compliance

DFP: deferiprone; DFX: deferasirox; SCD: sickle cell disease

Table 5. Study overview: Comparison 4. DFX film-coated tablet versus DFX dispersible tablet

Study	Participants	Intervention	Comparator	Outcomes
Taher 2017 ECLIPSE (multi-national)	Age > 10 years Thalassaemia and iron overload Thalassaemia major (81%)	DFX film-coated tablet as 90 mg, 180 mg and 360 mg for oral use n = 87	DFX dispersible tablet as 125 mg, 250 mg and 500 mg for oral use n = 86	13 and 24 weeks: Adherence Compliance Safety AEs

AEs: adverse events; DFX: deferasirox; SCD: sickle cell disease

Table 6. Study overview: Comparison 5. DFP and DFO versus DFP

Study	Participants	Intervention	Comparator	Outcomes
Aydinok 2007 Turkey	Age > 4 years β-thalassaemia (100%)	DFP + DFO (combined) DFO (50 mg/kg/day SC twice-weekly) combined with DFP (75 mg/kg/day, daily) n = 12 (8 analysed)	DFP 75 mg/kg/day, daily n = 12	12 months: Adherence LIC SF

Table 6. Study overview: Comparison 5. DFP and DFO versus DFP *(Continued)*

				QoL
Badawy 2010*	Age > 8 years	DFP, DFO	DFP	Adherence
Egypt	β-thalassaemia (100%)	Twice-weekly DFO (40 mg/kg/day)	75 mg/kg/day, daily	AEs
		DFP (75 mg/kg/day)	n = 50	
		n = 50		
El Beshlawy 2008	Age > 4 years	DFP + DFO	DFP	Adherence
Egypt	β-thalassaemia (100%)	DFP 60 to 83 mg/kg/day (daily) and DFO 23 to 50 mg/kg per dose (8 hours, 2 days/week)	60 to 83 mg/kg/day (daily)	Compliance
		n = 18	n = 18	Adverse events
				Iron overload
Maggio 2009	Age > 13 years	DFP-DFO (sequential treatment)	DFP	5 years:
Italy	Thalassaemia major (100%)	DFP 75 mg/kg, divided into 3 oral daily doses, for 4 days/week	75 mg/kg divided into 3 oral daily doses, daily	Adherence
		DFO SC infusion (8 to 12 hours) at 50 mg/kg/day for the remaining 3 days/week	n = 108	Survival
		n = 105		LIC & SF
				AEs

*Badawy 2010 did not report any outcomes by intervention group and did not include counts of events (i.e. AEs) and so was not included in the quantitative analysis.
Badawy 2010 and El Beshlawy 2008 are 3-arm trials (DFP, DFO vs DFP vs DFO) and so are listed in more than one comparison.
AE: adverse events; DFO: deferoxamine; DFP: deferiprone; LIC: liver iron content; QoL: quality of life; SC: subcutaneous; SF: serum ferritin

Table 7. Study overview: Comparison 6. DFP and DFO versus DFO

Study	Participants	Intervention	Comparator	Outcomes
Badawy 2010*	Age > 8 years	DFP, DFO	DFO	Adherence
Egypt	β-thalassaemia (100%)	Twice-weekly DFO (40 mg/kg/day)	40 mg/kg/day; 5 days/week	SF
		DFP (75 mg/kg/day)	n = 50	
		n = 50		
El Beshlawy 2008	Age > 4 years	DFP + DFO	DFO	54 weeks:
Egypt	β-thalassaemia (100%)	DFP 60 to 83 mg/kg/day (daily) and DFO 23 to 50 mg/kg per dose (8 hours, 2 days/week)	23 to 50 mg kg/day for 5 days/week	Adherence/compliance
		n = 18	n = 20	Adverse events (chelation-related SAEs)
				Iron overload
				Other AEs
				SAEs not reported

Table 7. Study overview: Comparison 6. DFP and DFO versus DFO *(Continued)*

Galanello 2006a Italy and Greece	Age > 10 years β-thalassaemia major (100%)	DFP + DFO DFO 20 to 60 mg/kg/day SC on 2 days a week with DFP 25 mg/kg/ body weight 3 x daily for 5 days/week n = 29	DFO 20 to 60 mg/kg/day subcutaneously on 5 to 7 days/week n = 30	12 months: Compliance LIC and SF AEs
Mourad 2003 Lebanon	Age 12 to 40 years β-thalassaemia	DFP + DFO DFP 75 mg/kg/day orally in 3 divided doses, 7 days/week, DFO by SC injection, daily dose of 2 g over 8 to 12 hours, 2 days/week n = 11	DFO SC injection, 40 to 50 mg/kg 8 to 12 hours a day, 5 to 7 days/week n = 14	1 year: Compliance Liver and renal function AEs (side effects)
Tanner 2007 Sardinia	Age > 18 years β-thalassaemia	DFP + DFO DFO 40 to 50 mg/kg SC for 5 days/week with DFP 75 mg/kg daily for 7 days/ week n = 28	DFO 40 to 50 mg/kg SC for 5 days/week with an oral placebo n = 30	1 year: compliance LIC and SF AEs

*Badawy 2010 did not report any outcomes by intervention group and did not include counts of events (i.e. AEs) and so was not included in the quantitative analysis.
Badawy 2010 and El Beshlawy 2008 are 3-arm trials (DFP, DFO vs DFP vs DFO) and so are listed in more than one comparison.
AE: adverse events; DFO: deferoxamine; DFP: deferiprone; LIC: liver iron content; QoL: quality of life; SAE: serious adverse events; SC: subcutaneous; SF: serum ferritin

Table 8. Study overview: Comparison 7. DFP/DFO versus DFP/DFX

Study	Participants	Intervention	Comparator	Outcomes
Elalfy 2015 Egypt and Oman	Age 10 to 18 years β-thalassaemia major	DFP/DFO DFP 75 mg/kg/day divided into 2 doses taken orally for 7 days (with 6- to 8-hour interval between the 2 doses) with DFO 40 mg/kg/day by SC infusion over 10 hours starting at 10 p.m. for 6 days/week n = 48	DFP/DFX DFP 75 mg/kg/day, divided into 2 doses taken orally with DFX 30 mg/kg/day taken orally at 10 p.m. for 7 days/week n = 48	1 year: Adherence LIC and SF SAEs and AEs Compliance Satisfaction QoL

AE: adverse events; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; LIC: liver iron content; QoL: quality of life; SAE: serious adverse events; SC: subcutaneous; SF: serum ferritin

Table 9. Study overview: Comparison 8. Medication management versus standard care

Study	Participants	Intervention	Comparator	Outcomes

Table 9. Study overview: Comparison 8. Medication management versus standard care *(Continued)*

Bahnasawy 2017	Age 8 to 18 years	Medication management	Standard care	6 months:
Egypt	β-thalassaemia major (100%)	n = 24	n = 24	Adherence
				SF
				QoL

QoL: quality of life; SF: serum ferritin

Table 10. Study overview: Comparison 9. Education versus standard care

Study	Participants	Intervention	Comparator	Outcomes
Gharaati 2019*	Age > 13 years	Education	Standard care	1 month:
Iran	Thalassaemia major	6 x 15- to 18-minute calls within a month	n = 45	Use of chelation therapy
		n = 46		

*Gharaati 2019 was not included in the quantitative analysis due to significant baseline imbalance (assessed using ROBINS-I for non RCTs).

Table 11. Overview of studies awaiting classification

Study	Reason for classification	Participants (inclusion criteria)	Intervention	Comparator	Outcomes
Medication interventions – RCTs only					
Bhojak 2020 RCT; N = 32; India Expected start date: 1 Sept 2017 Expected end date: NR (6 month duration)	Full publication available: mentions greater compliance in IV group in discussion, but no data provided Randomised but severe baseline imbalance in serum ferritin Unclear trial design: significant differences between trial registration and publication (study design randomised or observational, and focus on adherence or not); contacted authors for further information	3 to 18 years Thalassaemia patients on regular DFX	DFX, oral 15 to 40 mg/kg/day	DFO, injection, 20 to 40 mg/kg monthly	• Serum ferritin • Side effects • Cost • Compliance
CTRI/2020/07/026771 RCT; N = 45; India Start date: 30 July 2020 End date: 10 August 2021	Unclear trial design (not designed to measure adherence?) No publications or data	10 to 18 years Beta thalassaemia patients taking DFX	Combined DFP (75 mg/kg/day) + DFX (30 mg/kg/day), oral	DFX (30 mg/kg/day), oral	• Cardiac function • Kidney and liver function • Serum ferritin
EUCTR 2017-003777-34-NL (NL6659, PPI Shine Again)	Completed, some results available (May 2022), but results presented without subgrouping, and so cannot extract only SCD and thalas-	18+ years Hereditary anaemia (non-transfusion	PPI: esomeprazole (oral capsule)	Placebo	• Liver iron concentration

Table 11. Overview of studies awaiting classification *(Continued)*

RCT (cross-over); N = 30; The Netherlands End date: 12 April 2021	saemia data – awaiting publication of further results and contacted authors for further information	dependent); secondary haemochromatosis			• QoL (EQ-5D) • Compliance to study drug • Need for iron chelation therapy
Eghbali 2019 RCT; N = 50; Iran Start date: 22 September 2016 End date: 22 May 2017	Full publication available: mentions compliance with chelators was "acceptable", but no data provided Unclear trial design: significant differences between trial registration and publication (trial design randomised or observational); contacted authors for further information Would be a new comparison if included: DFO + DFX vs DFX	5 to 18 years Thalassaemia major	Combined DFO (Desferal ampoule) 50 mg/kg subcutaneously with Desferal pump, and DFX (Exjade) 30 mg/kg/day	DFX (Exjade) 30 mg/kg/day	• Serum ferritin • Compliance with chelators • Adverse events • Mortality
IRCT 2016 0310026998N7 RCT; N = 54; Iran Expected start date: 21 January 2018 Expected end date: 21 September 2018	Unclear trial design (not designed to measure adherence?) No publications or data	12+ years People with β-thalassaemia receiving DFO plus DFP	DFX plus DFP (n = 27)	DFO plus DFP (n = 27)	• SF • Liver iron concentration • QoL (SF-36)
IRCT 2019 0106042262N1 RCT; N = 107; Iran Start date: 19 February 2018 End date: 21 December 2018	Unclear trial design (not designed to measure adherence?) No publications or data	10+ years Transfusion-dependent β-thalassaemia	DFX (20 to 40 mg/kg daily) plus DFP (15 mg/kg/dose)	DFO (20 to 50 mg/kg daily with a pump) plus DFP (15 mg/kg/dose)	• Serum ferritin • Kidney and liver function
NCT00004982 Start date: December 1998 End date: November 2002	Unclear trial design (not designed to measure adherence?) No publications or data	7+ years Iron overload and thalassaemia	Various combinations of experimental iron chelating drugs	Standard care	• NR
Non-medication interventions – RCTs, NRSIs, CBA, ITS, repeated measures					
EX-PAT 2013 NRSI; N = 86; Turkey	No information on inclusion/exclusion criteria	People using DFX (unclear diagnoses)	Education (n = 45)	Standard care (n = 41)	• Compliance/ persistence

Table 11. Overview of studies awaiting classification *(Continued)*

Intervention from February to June 2009; follow-up to one year *Abstract only*	No publications or data				
Crosby 2019 Feasibility study; N = 18; USA *Abstract only*	Unclear trial design (single arm); part of larger study of self-management interventions No publications or data	13 to 21 years SCD	Electronic monitoring bottles	Unclear	• Adherence
IRCT 2013 042213092N1 RCT; N = 70; Iran Start date: 20 June 2013 Expected end date: 21 September 2013	Unclear trial design (not designed to measure adherence?) No publications or data	15 to 25 years Thalassaemia major	Education	Standard care	• QoL • Empowerment
IRCT 2019 0827044634N1 RCT; N = 60; Iran Expected start date: 11 September 2019 Expected end date (recruitment): 11 December 2019	Unclear if relevant intervention No publications or data	14 - 18 years β-thalassaemia major	Hope Therapy programme	Standard care	• Adherence to treatment • Hope
IRCT 2020 0126046270N1 Pre/post-test or NRSI; N = 47; Iran Start date: 25 September 2019 End date: 21 January 2020	Unclear trial design (not designed to study adherence?) No publications or data	8 - 18 years Thalassaemia major	Psycho-educational group sessions (n = 25)	Standard care (pre-test only)	• Anxiety • Loneliness
IRCT 2020 0606047670N2021 RCT; N = 34; Iran Expected start date: 20 December 2020 Expected end date: 17 February 2021	Unclear trial design (not designed to assess adherence?) No publications or data	15 to 20 years Thalassaemia major	Religious education	No intervention	• Life expectancy • Mental health • Spiritual health

CBA: controlled before-after studies; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; ITS: interrupted time series; IV: intravenous; NR: not reported; NRSI: non-randomised studies of interventions; PPI: proton pump inhibitor; QoL: quality of life; RCT: randomised controlled trial; SCD: sickle cell disease; SF: serum ferritin

Table 12. Overview of ongoing studies

Study	Participants (inclusion criteria)	Intervention	Comparator	Outcomes
Medication interventions - RCTs only				
CALYPSO NCT02435212 Multi-country RCT; N =2 24 Expected start: 21 October 2015 Expected end: 19 December 2023	2 to 18 years Any transfusion-dependent anaemia	DFX granule formulation; 14 mg/kg/day; 48 weeks	DFX DT formulation; 20 mg/kg/day; 48 weeks	• Compliance • Change in serum ferritin • Satisfaction • Overall safety
IRCT2015101218603N2 Country: Iran RCT; N = 100 Expected start: 22 December 2015 Expected end: NR	2+ years Transfusion-dependent beta-thalassaemia	DFX (new formulation Jadenu) 14 to 28 mg/kg/day orally	DFX (Exjade) 20 to 40 mg/kg/day orally	• Compliance • SF levels • Safety • GI effects
Non-medication interventions – RCTs, NRSIs, CBA, ITS, repeated measures				
Madderom 2016 (TEAM) NTR4750 (NL42182.000.12) Country: The Netherlands RCT; N = 100 Expected start: January 2013 Expected end: NR	All ages Homozygous or compound heterozygous sickle cell disease	Group medical appointments	Individual appointments (standard care)	• Self-efficacy • Adherence • QoL (SF-36)
NCT04877054 Country: USA RCT; N = 16 Expected start: 30 December 2021 Expected end: 1 August 2022	13 to 22 years Sickle cell disease	Telehealth (inc psycho-medical education and motivational interviewing) 1/week for 4 sessions	Education only (single session)	• Adherence • Feasibility • Acceptability

CBA: controlled before-and-after study; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; DT: dispersible tablet; GI: gastrointestinal; ITS: interrupted time series; NRSI: non-randomised studies of interventions; QoL: quality of life; RCT: randomised controlled trial; SF: serum ferritin

Table 13. HRQoL (Kwiatkowski 2021)

	DFP		DFO	
	n	Mean (SD)	n	Mean (SD)

Table 13. HRQoL (Kwiatkowski 2021) *(Continued)*

CHQ-50 physical (12-month change)	60	29.3 (13.94)	23	30.5 (11.51)
CHQ-50 psychosocial (12-month change)	60	42.5 (11.62)	23	41.3 (10.07)
SF-36 physical (12-month change)	35	43.1 (10.65)	19	43.0 (8.72)
SF-36 mental (12-month change)	35	44.7 (15.97)	19	40.9 (12.64)

CHQ-50: Child Health Questionnaire - 50 items; DFO: deferoxamine; DFP: deferiprone; HRQoL: health-related quality of life; SD: standard deviation; SE: standard error; SF-36: 36-item Short Form Survey
No significant between-group differences. Major bias due to missing data (over half) for outcomes (DFP 152 at baseline; DFO 76 at baseline). Data presented as mean (SE) in publication, converted to SD here.

APPENDICES

Appendix 1. Search strategies

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

#33 #9 and #17 and #32
#34 ((thalassemi* or thalassaemi* or sickle or hemoglobinopath* or haemoglobinopath*) and (adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or educat*)):ti
#35 #33 or #34

PubMed (for Epub Ahead of Print, In-Process & Other Non-Indexed Citations only)
#1 ((adher* OR nonadher* OR complian* OR comply* OR noncomplian* OR noncomply* OR complier* OR noncomplier* OR accept* OR nonaccept* OR abandon* OR co-operat* OR cooperat* OR unco-operative* OR uncooperative* OR nonco-operat* OR noncooperat* OR satisfaction OR dissatisfaction OR persist* OR educat* OR questionnaire*) AND (patient OR patients OR treatment* OR therapy OR therapies OR medication* OR drug*))
#2 (patient dropout* OR patient drop* outs OR patients drop* out OR treatment* refus* OR refus* treatment*)
#3 #1 OR #2
#4 (deferoxamine* OR deferoximine* OR deferrioxamine* OR desferioximine* OR desferrioxamine* OR desferroxamine* OR desferal* OR desferral* OR DFO OR desferin* OR desferol* OR dfom OR deferiprone OR L1 OR kelfer OR DMHP OR ferriprox OR CP20 OR dmohpo OR hdmpp CPD OR hdpp OR exjade* OR deferasirox* OR ICL 670* OR icl670* OR CGP "72670" OR iron chelat* OR iron reduc* OR chelat* treatment* OR chelat* therapy)
#5 (thalassemi* OR thalassaemi* OR lepore OR hydrops fetalis OR cooley* anemi* OR cooley* anaemi*)
#6 (hemoglobin disease OR haemoglobin disease OR hemochromatosis OR haemochromatosis OR hemosiderosis OR haemosiderosis)
#7 (mediterranean anemi* OR mediterranean anaemi* OR erythroblastic anemi* OR erythroblastic anaemi*)
#8 hemoglobinopath* OR haemoglobinopath* OR iron overload* OR iron over-load*
#9 ("sickle cell" OR sicklemi* OR sickled OR sickling OR meniscocyt* OR drepanocyt* OR "hemoglobin S" OR "hemoglobin SC" OR "hemoglobin SE" OR "hemoglobin SS" OR "hemoglobin C" OR "hemoglobin D" OR "haemoglobin S" OR "haemoglobin SC" OR "haemoglobin SE" OR "haemoglobin SS" OR "haemoglobin C" OR "haemoglobin D" OR "Hb S" OR "Hb SC" OR "Hb SE" OR "Hb SS" OR "Hb C" OR "Hb D" OR "SC disease")
#10 #5 OR #6 OR #7 OR #8 OR #9
#11 #3 AND 4 AND #10
#12 ((adher*[TI] OR nonadher*[TI] OR complian*[TI] OR comply*[TI] OR noncomplian*[TI] OR noncomply*[TI] OR complier*[TI] OR noncomplier*[TI] OR accept*[TI] OR nonaccept*[TI] OR abandon*[TI] OR co-operat*[TI] OR cooperat*[TI] OR unco-operative*[TI] OR uncooperative*[TI] OR nonco-operat*[TI] OR noncooperat*[TI] OR satisfaction[TI] OR dissatisfaction[TI] OR persist*[TI] OR educat*[TI] OR questionnaire*[TI]) AND (thalassemia*[TI] OR thalassaemia*[TI] OR sickle[TI] OR iron overload*[TI]))
#13 #11 OR #12
#14 (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])
#15 #13 AND #14

MEDLINE (Ovid)
1. exp "Patient Acceptance of Health Care"/
2. (px or ed).fs.
3. "Patient Education as Topic"/
4. exp Data Collection/
5. (adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or abandon* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or persist* or educat* or questionnaire*).ti.
6. ((adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or abandon* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or persist* or educat* or questionnaire*) adj6 (patient* or treatment* or therapy or therapies or medication* or drug*)).ab,kf.
7. (patient* adj3 (dropout* or drop* out*)).tw,kf.
8. Treatment Refusal/
9. (treatment* adj3 refus*).tw,kf.
10. or/1-9
11. exp IRON CHELATING AGENTS/
12. CHELATION THERAPY/
13. (chelation adj3 (treatment* or therap*)).tw,kf.
14. (deferoxamine* or deferoximine* or deferrioxamine* or desferioximine* or desferrioxamine* or desferroxamine* or desferal* or desferral* or DFO or desferin* or desferol* or dfom).mp.
15. (deferiprone or L1* or kelfer or DMHP or ferriprox or CP20 or dmohpo or hdmpp CPD or hdpp).mp.
16. (exjade* or deferasirox* or ICL 670* or icl670* or "CGP 72670").mp.
17. (iron adj5 (chelat* or reduc*)).tw,kf.
18. or/11-17
19. exp THALASSEMIA/
20. (thalass?emi* or lepore or hydrops fetalis).tw,kf.
21. ((hemoglobin or haemoglobin) adj3 disease).tw,kf.

22. (hemochromatosis or haemochromatosis or hemosiderosis or haemosiderosis).tw,kf.
23. ((mediterranean or erythroblastic or cooley*) adj (anemi* or anaemi*)).tw,kf.
24. exp IRON OVERLOAD/
25. (iron adj3 (overload* or over-load*)).tw,kf.
26. exp HEMOGLOBINOPATHIES/
27. exp HEMOGLOBIN, SICKLE/
28. (hemoglobinopath* or haemoglobinopath*).tw,kf.
29. exp ANEMIA, SICKLE CELL/
30. (barts and (blood or plasma)).tw,kf.
31. (sickle or sicklemi* or sickled or sickling or meniscocyt* or drepanocyt*).tw,kf.
32. (h?emoglobin s or h?emoglobin sc or h?emoglobin se or h?emoglobin ss or h?emoglobin c or h?emoglobin d or Hb s or Hb sc or Hb se or Hb ss or Hb c or Hb d or sc disease*).tw,kf.
33. or/19-32
34. 10 and 18 and 33
35. exp *Hemoglobinopathies/ or (thalass?emi* or sickle or hemoglobinopath* or haemoglobinopath*).ti.
36. exp *Patient Compliance/ or (adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or educat*).ti.
37. 35 and 36
38. 34 or 37

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

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

CINAHL (EBSCO*Host*)
S1 (MH "Patient Compliance+")
S2 (MH "Patient Education")
S3 (MH "Instrument by Type+")
S4 TI (adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or abandon* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or persist* or educat* or questionnaire*)
S5 AB ((adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or abandon* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or persist* or educat* or questionnaire*) N6 (patient* or treatment* or therapy or therapies or medication* or drug*))
S6 TX (patient* N3 (dropout* or drop* out*))
S7 MH Treatment Refusal
S8 TX (treatment* N3 refus*)
9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S10 (MH "Chelating Agents+")
S11 (MH "Chelation Therapy")
S12 TX (deferoxamine* or deferoximine* or deferrioxamine* or desferioximine* or desferrioxamine* or desferroxamine* or desferal* or desferral* or DFO or desferin* or desferol* or dfom)
S13 TX (deferiprone or L1* or kelfer or DMHP or ferriprox or CP20 or dmohpo or hdmpp CPD or hdpp)
S14 TX (exjade* or deferasirox* or ICL 670* or icl670* or "CGP 72670")
S15 TX (iron N5 (chelat* or reduc*)) OR TX (chelat* N3 (treatment* or therap*))
S16 S10 OR S11 OR S12 OR S13 OR S14 OR S15
S17 (MH "Thalassemia+")
S18 TX (thalassemi* or thalassaemi* or lepore or hydrops fetalis)
S19 TX ((hemoglobin or haemoglobin) N3 disease)
S20 TX (hemochromatosis or haemochromatosis or hemosiderosis or haemosiderosis)
S21 TX ((mediterranean or erythroblastic or cooley*) N1 (anemi* or anaemi*))
S22 (MH "Iron Overload+")
S23 TX (iron N3 (overload* or over-load*))
S24 (MH "Hemoglobinopathies")
S25 TX (hemoglobinopath* or haemoglobinopath*)
S26 (MH "Anemia, Sickle Cell+")
S27 TX (barts and (blood or plasma))
S28 TX (sickle OR sicklemi* OR sickled OR sickling OR meniscocyt* OR drepanocyt* OR "hemoglobin S" OR "hemoglobin SC" OR "hemoglobin SE" OR "hemoglobin SS" OR "hemoglobin C" OR "hemoglobin D" OR "haemoglobin S" OR "haemoglobin SC" OR "haemoglobin SE" OR "haemoglobin SS" OR "haemoglobin C" OR "haemoglobin D" OR "Hb S" OR "Hb SC" OR "Hb SE" OR "Hb SS" OR "Hb C" OR "Hb D" OR "SC disease")
S29 S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28
S30 S9 AND S16 AND S29
S31 (MM "Patient Compliance+")
S32 TI (adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or educat*)
S33 S31 OR S32
S34 (MM "Hemoglobinopathies+")
S35 TI (thalassemi* or thalassaemi* or sickle or hemoglobinopath* or haemoglobinopath*)
S36 S34 OR S35
S37 S33 AND S36
S38 S30 OR S37

APA PsycInfo (Ovid)
1. Treatment Compliance/ or Treatment Dropouts/ or Treatment Refusal/
2. Treatment Termination/
3. Client Education/
4. Questionnaires/ or General Health Questionnaire/

5. (adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or abandon* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or persist* or educat* or questionnaire*).ti.
6. ((adher* or nonadher* or complian* or comply* or noncomplian* or noncomply* or complier* or noncomplier* or accept* or nonaccept* or abandon* or co-operat* or cooperat* or unco-operative* or uncooperative* or nonco-operat* or noncooperat* or satisfaction or dissatisfaction or persist* or educat* or questionnaire*) adj6 (patient* or treatment* or therapy or therapies or medication* or drug*)).ab.
7. (patient* adj3 (dropout* or drop* out*)).tw.
8. (treatment* adj3 refus*).tw.
9. or/1-8
10. Sickle Cell Disease/
11. (sickle or sicklemi* or sickled or sickling or meniscocyt* or drepanocyt*).tw.
12. (h?emoglobin s or h?emoglobin sc or h?emoglobin se or h?emoglobin ss or h?emoglobin c or h?emoglobin d or Hb s or Hb sc or Hb se or Hb ss or Hb c or Hb d or sc disease*).tw.
13. (thalass?emi* or lepore or hydrops fetalis).tw.
14. ((hemoglobin or haemoglobin) adj3 disease).tw.
15. (hemochromatosis or haemochromatosis or hemosiderosis or haemosiderosis).tw.
16. ((mediterranean or erythroblastic or cooley*) adj (anemi* or anaemi*)).tw.
17. (hemoglobinopath* or haemoglobinopath*).tw.
18. (iron adj3 (overload* or over-load*)).tw.
19. (barts and (blood or plasma)).tw.
20. or/10-19
21. 9 and 20

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ti(adher* OR nonadher* OR complian* OR comply* OR noncomplian* OR noncomply* OR complier* OR noncomplier* OR accept* OR nonaccept* OR abandon* OR co-operat* OR cooperat* OR unco-operative* OR uncooperative* OR nonco-operat* OR noncooperat* OR satisfaction OR dissatisfaction OR refus* OR persist* OR educat* OR questionnaire*) AND ti(thalassemia OR thalassaemia OR sickle OR sickled OR sickling OR iron overload OR hemoglobinopath*) AND (chelation OR chelating OR deferiprone OR deferoxamine OR deferasirox OR DFO OR ferriprox OR exjade OR iron reduction)

Web of Science CPCI-S & CPSSI

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

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Other Terms: (thalassemia OR sickle cell anemia OR iron overload OR hemoglobinopathies) AND (iron chelation OR chelation therapy OR deferiprone OR deferoxamine OR deferasirox OR DFO OR iron reduction)

WHO ICTRP

Condition: thalassemia OR sickle cell anemia OR iron overload OR hemoglobinopathies
Intervention: iron chelation OR chelation therapy OR deferiprone OR deferoxamine OR deferasirox OR DFO OR iron reduction

ISRCTN
Condition: thalassemia OR sickle cell anemia OR iron overload OR hemoglobinopathies
Interventions: iron chelation OR chelation therapy OR deferiprone OR deferoxamine OR deferasirox OR DFO OR iron reduction

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

ROBINS-I tool (Stage I)

Specify the review question

Participants	
Experimental intervention	
Control intervention	
Outcomes	

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

Specify a target trial specific to the study.

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

Is your aim for this study...?

☐ to assess the effect of initiating intervention (as in an intention-to-treat analysis)

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

Specify the outcome

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

Specify the numerical result being assessed

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

Preliminary consideration of confounders

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

'Important' confounding areas are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. 'Validity' refers to whether the confounding variable or variables fully measure the area, while 'reliability' refers to the precision of the measurement (more measurement error means less reliability).

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

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

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

Preliminary consideration of co-interventions

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

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

(i) Co-interventions listed in the review protocol		
Co-intervention	Is there evidence that controlling for this co-intervention was	Is presence of this co-intervention likely to favour outcomes in the experimental or the control group

(Continued)

	unnecessary (e.g. because it was not administered)?	
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information

(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important

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

Risk of bias assessment (cohort-type studies)

Bias domain	Signalling questions	Elaboration	Response options
Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	In rare situations, such as when studying harms that are very unlikely to be related to factors that influence treatment decisions, no confounding is expected and the study can be considered to be at low risk of bias due to confounding, equivalent to a fully randomised trial.	Y / PY / PN / N
	If**N** or **PN** to**1.1**: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	There is no NI (No information) option for this signalling question.	
	If **Y** or **PY** to **1.1**: determine whether there is a need to assess time-varying confounding:		
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	If participants could switch between intervention groups then associations between intervention and outcome may be biased by time-varying confounding. This occurs when prognostic factors influence switches between intended interventions.	NA / Y / PY / PN / N / NI

(Continued)

If **N** or**PN**, answer questions relating to baseline confounding (1.4 to 1.6) If **Y** or**PY**, proceed to question 1.3.		
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? If **N** or **PN**, answer questions relating to baseline confounding (1.4 to 1.6) If **Y** or**PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	If intervention switches are unrelated to the outcome, for example when the outcome is an unexpected harm, then time-varying confounding will not be present and only control for baseline confounding is required.	NA / Y / PY / PN / N / NI
Questions relating to baseline confounding only		
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding areas?	Appropriate methods to control for measured confounders include stratification, regression, matching, standardization, and inverse probability weighting. They may control for individual variables or for the estimated propensity score. Inverse probability weighting is based on a function of the propensity score. Each method depends on the assumption that there is no unmeasured or residual confounding.	NA / Y / PY / PN / N / NI
1.5.**If Y** or **PY** to**1.4**: were confounding areas that were controlled for measured validly and reliably by the variables available in this study?	Appropriate control of confounding requires that the variables adjusted for are valid and reliable measures of the confounding domains. For some topics, a list of valid and reliable measures of confounding domains will be specified in the review protocol but for others such a list may not be available. Study authors may cite references to support the use of a particular measure. If authors control for confounding variables with no indication of their validity or reliability pay attention to the subjectivity of the measure. Subjective measures (e.g. based on self-report) may have lower validity and reliability than objective measures such as lab findings.	NA / Y / PY / PN / N / NI
1.6. Did the authors control for any post-intervention variables?	Controlling for post-intervention variables is not appropriate. Controlling for mediating variables estimates the direct effect of intervention and may introduce confounding. Controlling for common effects of intervention and outcome causes bias.	NA / Y / PY / PN / N / NI
Questions relating to baseline and time-varying confounding		
1.7. Did the authors use an appropriate analysis method	Adjustment for time-varying confounding is necessary to estimate per-protocol effects in both randomised trials and NRSI. Appropriate methods include those based on inverse-probabil-	NA / Y / PY / PN / N / NI

(Continued)

	that adjusted for all the important confounding areas and for time-varying confounding?	ity weighting. Standard regression models that include time-updated confounders may be problematic if time-varying confounding is present.	
	1.8. If**Y** or**PY** to**1.7**: Were confounding areas that were adjusted for measured validly and reliably by the variables available in this study?	See 1.5 above.	NA / Y / PY / PN / N / NI
	Risk of bias judgement	**Low** - no confounding expected. **Moderate** - confounding expected, all known important confounding domains appropriately measured and controlled for; and Reliability and validity of measurement of important domains were sufficient, such that we do not expect serious residual confounding. **Serious** - at least one known important domain was not appropriately measured, or not controlled for; or Reliability or validity of measurement of a important domain was low enough that we expect serious residual confounding. **Critical** - confounding inherently not controllable, or the use of negative controls strongly suggests unmeasured confounding.	Low / Moderate / Serious / Critical / NI
	Optional: what is the predicted direction of bias due to confounding?	Can the true effect estimate be predicted to be greater or less than the estimated effect in the study because one or more of the important confounding domains was not controlled for? Answering this question will be based on expert knowledge and results in other studies and therefore can only be completed after all of the studies in the body of evidence have been reviewed. Consider the potential effect of each of the unmeasured domains and whether all important confounding domains not controlled for in the analysis would be likely to change the estimate in the same direction, or if one important confounding domain that was not controlled for in the analysis is likely to have a dominant impact.	Favours experimental / Favours comparator / Unpredictable
Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	This domain is concerned only with selection into the study based on participant characteristics observed after the start of intervention. Selection based on characteristics observed before the start of intervention can be addressed by controlling for imbalances between intervention and control groups in baseline characteristics that are prognostic for the outcome (baseline confounding).	Y / PY / PN / N / NI
	If**N** or**PN** to**2.1**: go to 2.4		

(Continued)

2.2. If**Y** or**PY** to**2.1**: were the post-intervention variables that influenced selection likely to be associated with intervention	Selection bias occurs when selection is related to an effect of either intervention or a cause of intervention and an effect of either the outcome or a cause of the outcome. Therefore, the result is at risk of selection bias if selection into the study is related to both the intervention and the outcome.	NA / Y / PY / PN / N / NI
2.3 If **Y** or**PY** to**2.2:** were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		NA / Y / PY / PN / N / NI
2.4. Do start of follow up and start of intervention coincide for most participants?	If participants are not followed from the start of the intervention then a period of follow up has been excluded, and individuals who experienced the outcome soon after intervention will be missing from analyses. This problem may occur when prevalent, rather than new (incident), users of the intervention are included in analyses.	Y / PY / PN / N / NI
2.5. If**Y** or**PY** to**2.2** and**2.3**, or **N** or**PN to 2.4**: were adjustment techniques used that are likely to correct for the presence of selection biases?	It is in principle possible to correct for selection biases, for example by using inverse probability weights to create a pseudo-population in which the selection bias has been removed, or by modelling the distributions of the missing participants or follow up times and outcome events and including them using missing data methodology. However such methods are rarely used and the answer to this question will usually be “No”	NA / Y / PY / PN / N / NI
Risk of bias judgement	**Low** - all participants who would have been eligible for the target trial were included in the study and start of follow up and start of intervention coincide for all subjects.	Low / Moderate / Serious / Critical / NI
	Moderate - selection into the study may have been related to intervention and outcome, but the authors used appropriate methods to adjust for the selection bias; or Start of follow up and start of intervention do not coincide for all participants, but (a) the proportion of participants for which this was the case was too low to induce important bias; (b) the authors used appropriate methods to adjust for the selection bias; or (c) the review authors are confident that the rate (hazard) ratio for the effect of intervention remains constant over time.	
	Serious - selection into the study was related to intervention and outcome; or Start of follow up and start of intervention do not coincide, and a potentially important amount of follow-up time is missing from analyses, and the rate ratio is not constant over time.	
	Critical - selection into the study was strongly related to intervention and outcome; or	

(Continued)

		A substantial amount of follow-up time is likely to be missing from analyses, and the rate ratio is not constant over time.	
	Optional: what is the predicted direction of bias due to selection of participants into the study?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable
Bias in classification of interventions	3.1 Were intervention groups clearly defined?	A pre-requisite for an appropriate comparison of interventions is that the interventions are well defined. Ambiguity in the definition may lead to bias in the classification of participants. For individual-level interventions, criteria for considering individuals to have received each intervention should be clear and explicit, covering issues such as type, setting, dose, frequency, intensity and/or timing of intervention. For population-level interventions (e.g. measures to control air pollution), the question relates to whether the population is clearly defined, and the answer is likely to be 'Yes'.	Y / PY / PN / N / NI
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	In general, if information about interventions received is available from sources that could not have been affected by subsequent outcomes, then differential misclassification of intervention status is unlikely. Collection of the information at the time of the intervention makes it easier to avoid such misclassification. For population-level interventions (e.g. measures to control air pollution), the answer to this question is likely to be 'Yes'.	Y / PY / PN / N / NI
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Collection of the information at the time of the intervention may not be sufficient to avoid bias. The way in which the data are collected for the purposes of the NRSI should also avoid misclassification.	Y / PY / PN / N / NI
	Risk of bias judgement	**Low** - intervention status is well defined and based solely on information collected at the time of intervention.	Low / Moderate / Serious / Critical / NI
		Moderate - intervention status is well defined but some aspects of the assignments of intervention status were determined retrospectively	
		Serious - intervention status is not well defined, or major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome.	
		Critical - (unusual) An extremely high amount of misclassification of intervention status, e.g. because of unusually strong recall biases.	
	Optional: what is the predicted direction of bias due to measurement of	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

(Continued)

	outcomes or interventions?		
Bias due to departures from intended interventions	4.1. Was the intervention implemented successfully for most participants?	Consider the success of implementation of the intervention in the context of its complexity. Was recommended practice followed by those administering the intervention?	Y / PY / PN / N / NI
	If your aim for this study is to assess the effect of initiating and adhering to intervention (as in a per-protocol analysis), answer questions 4.2 to 4.4		
	4.2. Did study participants adhere to the assigned intervention regimen?	Lack of adherence to assigned intervention includes cessation of intervention, crossovers to the comparator intervention and switches to another active intervention. We distinguish between analyses where: (1) intervention switches led to follow up time being assigned to the new intervention; and (2) intervention switches (including cessation of intervention) where follow up time remained allocated to the original intervention; (3) is addressed under time-varying confounding, and should not be considered further here. Consider available information on the proportion of study participants who continued with their assigned intervention throughout follow up. Was lack of adherence sufficient to impact the intervention effect estimate?	NA/ Y / PY / PN / N / NI
	4.3. Were important co-interventions balanced across intervention groups?	Consider the co-interventions that are likely to affect the outcome and to have been administered in the context of this study, based on the preliminary consideration of co-interventions and available literature. Consider whether these co-interventions are balanced between intervention groups.	NA/ Y / PY / PN / N / NI
	4.4. If**N** or**PN** to**4.1, 4.2** or**4.3**: were adjustment techniques used that are likely to correct for these issues?	Such adjustment techniques include inverse-probability weighting to adjust for censoring at deviation from intended intervention, or inverse probability weighting of marginal structural models to adjust for time-varying confounding. Specialist advice may be needed to assess studies that used these approaches.	NA / Y / PY / PN / N / NI
	Risk of bias judgement	**Low** - no bias due to deviation from the intended intervention is expected, for example if both the intervention and comparator are implemented over a short time period, and subsequent interventions are part of routine medical care, or if the specified comparison relates to initiation of intervention regardless of whether it is continued.	Low / Moderate / Serious / Critical / NI
		Moderate - bias due to deviation from the intended intervention is expected, and switches, co-interventions, and some problems with intervention fidelity are appropriately measured and adjusted for in the analyses. Alternatively, most (but not all) deviations from intended intervention reflect the natural course of events after initiation of intervention.	

(Continued)

		Serious - switches in treatment, co-interventions, or problems with implementation fidelity are apparent and are not adjusted for in the analyses.	
		Critical - substantial deviations from the intended intervention are present and are not adjusted for in the analysis.	
	Optional: what is the predicted direction of bias due to departures from the intended interventions?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable
Bias due to missing data	5.1 Were there missing outcome data?	This aims to elicit whether the proportion of missing observations is likely to result in missing information that could substantially impact our ability to answer the question being addressed. Guidance will be needed on what is meant by 'reasonably complete'. One aspect of this is that review authors would ideally try and locate an analysis plan for the study.	Y / PY / PN / N / NI
	5.2 Were participants excluded due to missing data on intervention status?	Missing intervention status may be a problem. This requires that the intended study sample is clear, which it may not be in practice.	Y / PY / PN / N / NI
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	This question relates particularly to participants excluded from the analysis because of missing information on confounders that were controlled for in the analysis.	Y / PY / PN / N / NI
	5.4 If **Y** or**PY to 5.1, 5.2** or**5.3**: are the proportion of participants and reasons for missing data similar across interventions?	This aims to elicit whether either (i) differential proportion of missing observations or (ii) differences in reasons for missing observations could substantially impact on our ability to answer the question being addressed.	NA / Y / PY / PN / N / NI
	5.5**If Y** or **PY** to**5.1, 5.2** or**5.3**: were appropriate statistical methods used to account for missing data?	It is important to assess whether assumptions employed in analyses are clear and plausible. Both content knowledge and statistical expertise will often be required for this. For instance, use of a statistical method such as multiple imputation does not guarantee an appropriate answer. Review authors should seek naïve (complete-case) analyses for comparison, and clear differences between complete-case and multiple imputation-based findings should lead to careful assessment of the validity of the methods used.	NA / Y / PY / PN / N / NI
	Risk of bias judgement	**Low** - data were reasonably complete; or Proportions of and reasons for missing participants were similar across intervention groups; or Analyses that addressed missing data are likely to have removed any risk of bias.	Low / Moderate / Serious / Critical / NI
		Moderate - proportions of missing participants differ across interventions; or Reasons for missingness differ minimally	

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		across interventions; and Missing data were not addressed in the analysis.	
		Serious - proportions of missing participants differ substantially across interventions; or Reasons for missingness differ substantially across interventions; and Missing data were addressed inappropriately in the analysis; or The nature of the missing data means that the risk of bias cannot be removed through appropriate analysis.	
		Critical - (unusual) There were critical differences between interventions in participants with missing data that were not, or could not, be addressed through appropriate analysis.	
	Optional: what is the predicted direction of bias due to missing data?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable
Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Some outcome measures involve negligible assessor judgment, e.g. all-cause mortality or non-repeatable automated laboratory assessments. Risk of bias due to measurement of these outcomes would be expected to be low.	Y / PY / PN / N / NI
	6.2 Were outcome assessors aware of the intervention received by study participants?	If outcome assessors were blinded to intervention status, the answer to this question would be 'No'. In other situations, outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators; the answer this question would then also be 'No'. In studies where participants report their outcomes themselves, for example in a questionnaire, the outcome assessor is the study participant. In an observational study, the answer to this question will usually be 'Yes' when the participants report their outcomes themselves.	Y / PY / PN / N / NI
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Comparable assessment methods (i.e. data collection) would involve the same outcome detection methods and thresholds, same time point, same definition, and same measurements	Y / PY / PN / N / NI
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	This question refers to differential misclassification of outcomes. Systematic errors in measuring the outcome, if present, could cause bias if they are related to intervention or to a confounder of the intervention-outcome relationship. This will usually be due either to outcome assessors being aware of the intervention received or to non-comparability of outcome assessment methods, but there are examples of differential misclassification arising despite these controls being in place.	Y / PY / PN / N / NI
	Risk of bias judgement	**Low** - the methods of outcome assessment were comparable across intervention groups; and The outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants (i.e. is	Low / Moderate / Serious / Critical / NI

(Continued)

		objective) or the outcome assessors were unaware of the intervention received by study participants; and Any error in measuring the outcome is unrelated to intervention status.	
		Moderate - the methods of outcome assessment were comparable across intervention groups; and The outcome measure is only minimally influenced by knowledge of the intervention received by study participants; and Any error in measuring the outcome is only minimally related to intervention status.	
		Serious - the methods of outcome assessment were not comparable across intervention groups; or The outcome measure was subjective (i.e. likely to be influenced by knowledge of the intervention received by study participants) and was assessed by outcome assessors aware of the intervention received by study participants; or Error in measuring the outcome was related to intervention status.	
		Critical - the methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups.	
	Optional: what is the predicted direction of bias due to measurement of outcomes?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable
Bias in selection of the reported result	Is the reported effect estimate unlikely to be selected, on the basis of the results, from...		
	7.1. ... multiple outcome *measurements* within the outcome domain?	For a specified outcome domain, it is possible to generate multiple effect estimates for different measurements. If multiple measurements were made, but only one or a subset is reported, there is a risk of selective reporting on the basis of results.	Y / PY / PN / N / NI
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	Because of the limitations of using data from non-randomized studies for analyses of effectiveness (need to control confounding, substantial missing data, etc), analysts may implement different analytic methods to address these limitations. Examples include unadjusted and adjusted models; use of final value vs change from baseline vs analysis of covariance; different transformations of variables; a continuously scaled outcome converted to categorical data with different cutpoints; different sets of covariates used for adjustment; and different analyt-	Y / PY / PN / N / NI

(Continued)

		ic strategies for dealing with missing data. Application of such methods generates multiple effect estimates for a specific outcome metric. If the analyst does not prespecify the methods to be applied, and multiple estimates are generated but only one or a subset is reported, there is a risk of selective reporting on the basis of results.	
	7.3 ... different *subgroups*?	Particularly with large cohorts often available from routine data sources, it is possible to generate multiple effect estimates for different subgroups or simply to omit varying proportions of the original cohort. If multiple estimates are generated but only one or a subset is reported, there is a risk of selective reporting on the basis of results.	Y / PY / PN / N / NI
	Risk of bias judgement	**Low** - there is clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses and sub-cohorts.	Low / Moderate / Serious / Critical / NI
		Moderate - the outcome measurements and analyses are consistent with an *apriori* plan; or are clearly defined and both internally and externally consistent; and there is no indication of selection of the reported analysis from among multiple analyses; and there is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results.	
		Serious - outcome measurements or analyses are internally or externally inconsistent; or There is a high risk of selective reporting from among multiple analyses; or The cohort or subgroup is selected from a larger study for analysis and appears to be reported on the basis of the results.	
		Critical - there is evidence or strong suspicion of selective reporting of results, and the unreported results are likely to be substantially different from the reported results.	
	Optional: What is the predicted direction of bias due to selection of the reported result?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable
Overall bias	**Risk of bias judgement**	**Low** - the study is judged to be at low risk of bias for all domains.	Low / Moderate / Serious / Critical / NI
		Moderate - the study is judged to be at low or moderate risk of bias for all domains.	

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

WHAT'S NEW

Date	Event	Description
3 March 2023	New citation required but conclusions have not changed	Five authors have stepped down from the review team: Patricia Fortin, Sheila Fisher, Karen Madgwick, Marialena Trivella and Sally Hopewell. A new author, Louise Geneen, has joined the author team and taken on the role of lead author. Conclusions have not changed from the previous version of the review.
3 March 2023	New search has been performed	We re-assessed trials previously listed as ongoing or awaiting classification, to ascertain whether or not they should be included. In this update we included four new trials: one newly identified non-randomised trial (Gharaati 2019), two trials previously listed as ongoing (Kwiatkowski 2021; Maggio 2020), and one trial (Calvaruso 2014) that had been incorrectly merged with another due to misreporting of trial registration numbers within the publications (Calvaruso 2015). We also identified two new ongoing trials, and 10 new trials are awaiting classification. Combined with the previous version of the review, this resulted in 20 trials being included in the qualitative synthesis (four are listed as ongoing and 13 are awaiting classification), of which we have included 18 trials in the quantitative analysis, as two trials did not provide sufficient usable data (Badawy 2010; Gharaati 2019).

HISTORY

Protocol first published: Issue 9, 2016
Review first published: Issue 5, 2018

CONTRIBUTIONS OF AUTHORS

The author contributions for the 2022 update were as listed below.

Lise Estcourt: selection of trials; eligibility assessment; content expert, and review content development.

Carolyn Doree: development of search strategies; all searches and de-duplication.

Louise Geneen: selection of trials; eligibility assessment; data extraction, risk of bias assessment and review content development; update of review text, tables and figures.

DECLARATIONS OF INTEREST

Louise Geneen: none to declare.

Carolyn Doree: none to declare.

Lise Estcourt: declares her employment as a healthcare professional by NHS Blood and Transplant.

SOURCES OF SUPPORT

Internal sources

- NHS Blood and Transplant, Research and Development, UK

  To fund the work of the Systematic Review Initiative (SRI)

External sources

- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

See Fortin 2016.

Confidence intervals

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

Assessment of reporting biases

Where trial protocols had been published, or registered, we were able to assess reporting bias, comparing planned outcome reporting and analyses to those published by the triallists.

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

Subgroup analysis

Due to insufficient data we could not undertake subgroup analyses as planned in the protocol:

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

Where different populations have been assessed, we have not pooled the data, and have instead presented as subgroups or single study data.

Sensitivity analysis

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

INDEX TERMS

Medical Subject Headings (MeSH)

*Anemia, Sickle Cell [complications] [drug therapy]; Chelating Agents; Chelation Therapy; Deferoxamine [adverse effects]; *Drug-Related Side Effects and Adverse Reactions; Iron; *Thalassemia

MeSH check words

Child; Humans