Health Technology Assessment 2009; Vol. 13: No. 1

Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation

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January 2009
DOI: 10.3310/hta13010

Health Technology Assessment
NIHR HTA Programme
www.hta.ac.uk

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Declared competing interests of authors: Professor Tom Walley is Director of the HTA Programme. His employer is reimbursed for time allocated to duties as Director. Dr Ade Olujohungbe has declared receiving honoraria from Novartis (manufacturer of deferoxamine and deferasirox) for consultancy, speaking and attending a symposium.

Published January 2009
DOI: 10.3310/hta13010

This report should be referenced as follows:

McLeod C, Fleeman N, Kirkham J, Bagust A, Boland A, Chu P, *et al*. Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation. *Health Technol Assess* 2009;**13**(1).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (*SciSearch*®) and *Current Contents*®/Clinical Medicine.

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The research reported in this issue of the journal was commissioned and funded by the HTA Programme on behalf of NICE as project number 06/12/01. The protocol was agreed in May 2007. The assessment report began editorial review in December 2007 and was accepted for publication in June 2008. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NCCHTA.

Printed on acid-free paper in the UK by the Charlesworth Group.

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Abstract

Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation

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Objectives: To assess the clinical effectiveness and cost-effectiveness of deferasirox for the treatment of iron overload associated with regular blood transfusions in patients with chronic anaemia such as beta-thalassaemia major (beta-TM) and sickle cell disease (SCD).
Data sources: Electronic databases were searched up to March 2007.
Review methods: Methods followed accepted procedures for conducting and reporting systematic reviews and economic evaluations.
Results: A total of 14 randomised controlled trials (RCTs) involving a study population of 1480 (ranging from 13 to 586) met the inclusion criteria. There was a high degree of heterogeneity between trials in terms of trial design and outcome reporting. As such it was only possible to meta-analyse serum ferritin data from six trials making comparisons between deferiprone and DFO and combination therapy and DFO. Only one of the results was statistically significant, favouring combination therapy over DFO alone for serum ferritin at 12 months. How this translates into iron loading in organs such as the heart is unclear, nor was it possible to determine the long-term benefits of chelation therapy. Eight full economic evaluations (one full paper; seven abstracts) were included in the review. The results were generally consistent and appear to demonstrate the cost-effectiveness of deferasirox compared with DFO for the treatment of iron overload in a number of different patient populations and study locations. However, a number of assumptions and, in the case of the long-term studies, extrapolation from short-term RCT data were required, which render the results highly speculative at best. Because of the paucity of long-term data we developed a simple, short-term (1 year) model to assess the costs and benefits of deferasirox, deferiprone and DFO in patients with beta-TM and SCD from an NHS perspective. A number of assumptions were required to generate results and, as such, they should be interpreted as indicative rather than factual. Our model suggests that deferasirox may be a cost-effective strategy compared with DFO, at a cost per quality-adjusted life-year (QALY) below £30,000 per year, for patients with beta-TM and SCD. However, this is highly dependent upon the age of the patient and the use and benefits of balloon infusers to administer DFO. Deferasirox compared with deferiprone is likely to be cost-effective only for young children. Furthermore, if deferiprone is proven to offer the same health benefits as deferasirox, the latter will not be cost-effective for any patient compared with deferiprone.
Conclusions: In the short term there is little clinical difference between any of the three chelators in terms

of removing iron from the blood and liver. Deferasirox may be cost-effective compared with DFO in patients with beta-TM and SCD, but it is unlikely to be cost-effective compared with deferiprone. Elucidating the long-term benefits of chelation therapy, including issues of adverse events and adherence, should be the primary focus for future research. Future work should aim for consistency and transparency in reporting study design and results to aid decision-making when making comparisons across trials.

Contents

Glossary and list of abbreviations

Glossary

Chelation This is the term used to refer to the binding of a compound to a metal ion. In the case of iron chelation, iron chelators (deferasirox, deferoxamine or deferiprone) are used to bind iron in the body. Once the iron is bound it can be more readily excreted from the body.

Cost effective Cost-effectiveness has numerous meanings; however, for practical purposes it is usually given to mean that the cost per quality-adjusted life-year gained is below a notional willingness to pay threshold. Currently in the UK a threshold of £20,000–30,000 is commonly used. Hence, for the purposes of this review we interpret ICERs below £20,000 as cost-effective, ICERs between £20,000 and £30,000 as possibly cost-effective and ICERs above £30,000 as unlikely to be cost-effective.

Erythropoiesis This is the process by which red blood cells (erythrocytes) are produced. In human adults this occurs in the bone marrow.

Sickle This is used to refer to the peculiar crescent shape formed by red blood cells in sickle cell disease.

SQUID (superconducting quantum interference devices) These are very sensitive magnetometers used to measure extremely small magnetic fields. They can be used to measure the amount of iron in the liver.

T2* This is a measure of iron in the body. It is measured indirectly using magnetic resonance imaging and is of use for detecting both liver and cardiac iron. The severity of iron loading is defined as follows: liver: none > 6.3 ms, mild 2.7–6.3 ms, moderate 1.4–2.7 ms, severe < 1.4 ms; heart: none > 20 ms, mild 14–20 ms, moderate 10–14 ms, severe < 10 ms.

List of abbreviations

AE	adverse events
ALT	alanine aminotransferase
AST	aspartate aminotransferase
beta-TM	beta-thalassaemia major
beta-TI	beta-thalassaemia intermediate
BNF	*British National Formulary*
CEA	cost-effectiveness analysis
CI	confidence interval
CMR	cardiac magnetic resonance imaging
CRD	Centre for Reviews and Dissemination
CUA	cost–utility analysis
DBA	Diamond Blackfan anaemia
DFO	deferoxamine/desferrioxamine
dw	dry weight
EMEA	European Agency for the Evaluation of Medicinal Products

FDA	US Food and Drug Administration
GI	gastrointestinal
ICER	incremental cost-effectiveness ratio
ICT	iron chelation therapy
ITT	intention to treat
LIC	liver iron concentration
LYG	life-years gained
MDS	myelodysplastic syndrome
MDS del(5q)	myelodysplastic syndrome with isolated del(5q)
MDS-U	myelodysplastic syndrome, unclassified
MR	magnetic resonance
MRI	magnetic resonance imaging
NCCHTA	National Coordinating Centre for Health Technology Assessment
OR	odds ratio
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QoL	quality of life
RA	refractory anaemia
RAEB-1	refractory anaemia with excess blasts-1
RAEB-2	refractory anaemia with excess blasts-2
RARS	refractory anaemia with ringed sideroblasts
RCMD	refractory cytopenia with multilineage dysplasia
RCMD-RS	refractory cytopenia with multilineage dysplasia and ringed sideroblasts
RCT	randomised controlled trial
SA	sensitivity analysis
SAE	severe adverse event
SCD	sickle cell disease
SD	standard deviation
SQUID	superconducting quantum interference device
WHO	World Health Organization
WMD	weighted mean difference

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Objectives

The review assessed the clinical effectiveness and cost-effectiveness of deferasirox for the treatment of iron overload in chronically transfused anaemic patients.

Comparisons were made between deferasirox and deferoxamine (DFO), deferiprone or placebo.

To ensure that the wider picture of iron-chelating therapy was considered, comparisons were also made between deferiprone (alone and in combination with DFO) and DFO (alone and in combination with deferiprone).

Background

Iron overload is a rare condition in which iron collects in the body. There are no natural means of removing excess iron from the body and so iron gradually accumulates (over 5–10 years) to toxic levels that affect major organs such as the heart and liver. Iron overload can be caused by a malabsorption of iron from the ingestion of food or more commonly through frequent blood transfusions. Blood transfusions represent life-saving therapy for patients with chronic anaemia, such as those suffering from thalassaemia and sickle cell disease (SCD). However, with each unit of transfused blood, 200–250 mg of iron is transferred to the patient. The risk of iron overload increases once patients have received approximately 20 transfusions.

The conventional treatment for transfusion-related iron overload is chelation therapy aimed at reducing iron stores or maintaining an iron balance. Treatment with iron chelators is primarily governed by the degree of iron overload and the transfusional requirements of patients.

Currently in the UK, patients presenting with transfusion-related iron overload are treated with DFO. Patients receive DFO via nightly infusions (5–7 times a week) from as early as 2 years of age. The regimen is not well tolerated, particularly in adolescents, and there is alleged to be a high degree of non-adherence to therapy, with resulting detrimental heath effects.

Patients over the age of 6 years who are suffering from beta-thalassaemia also have the option to try deferiprone. Deferiprone is an oral tablet given thrice daily, which limits the patient administration burden. However, it has been associated with adverse events such as neutropenia and agranulocytosis, which limits its use.

Deferasirox is a new orally active iron-chelating agent that is given once daily as a suspension (usually in water or fruit juice). Deferasirox may be of particular value in treating patients with iron overload who cannot tolerate DFO and who are not suitable for, or who are intolerant of, deferiprone.

Methods

The assessment was conducted according to accepted procedures for conducting and reporting systematic reviews and economic evaluations. Evidence on clinical effects and cost-effectiveness was identified using a comprehensive search strategy (for the period up to March 2007) of bibliographic databases (including the Cochrane Library, EMBASE, MEDLINE) as well as hand-searching activities. Unpublished evidence (such as conference abstracts) was considered for inclusion in the assessment. A number of trialists were also contacted for additional outcome data.

Inclusion criteria

Randomised controlled trials (RCTs) that compared deferasirox with DFO, deferiprone or placebo were considered for inclusion in the review. RCTs comparing deferiprone alone or in combination with DFO with DFO were also considered. The patient population was limited to patients suffering from chronic anaemia requiring regular blood transfusions. Data on the following outcome measures were considered: change in serum ferritin, change in liver iron concentration (LIC), cardiac iron (cardiac T2*), quality of life, and adverse effects of treatment.

Full economic evaluations that compared two or more chelation options and assessed both costs and consequences were considered for inclusion in the review. Only studies investigating patients with chronic anaemia requiring regular blood transfusions were considered.

Results

Clinical review

A total of 14 RCTs, making comparisons between deferasirox, deferoxamine (DFO), deferiprone and combination therapy (deferiprone and DFO) and involving a study population of 1480 (ranging from 13 to 586), met the inclusion criteria. Three RCTs comparing deferasirox with DFO were found although none contained data that could be included in the meta-analyses; there were no studies comparing deferasirox with deferiprone or combination therapy.

The majority of trials included patients with beta-thalassaemia major (beta-TM) or thalassaemia. The duration of each trial varied between 5 days and 2 years with the majority continuing for approximately 12 months. Most trials provided data on serum ferritin or liver iron concentration.

There was a high degree of heterogeneity between trials in terms of trial design and outcome reporting. As such it was only possible to meta-analyse serum ferritin data from six trials, making comparisons between deferiprone and DFO, and combination therapy and DFO.

In general it appears that there is little difference between chelation agents in terms of reducing serum ferritin. Only one of the results was statistically significant, favouring combination therapy over DFO alone for serum ferritin at 12 months. How this translates into iron loading in organs such as the heart is not clear, nor was it possible to determine the long-term benefits of chelation therapy.

Economic evaluation

Eight full economic evaluations (one full paper; seven abstracts) were included in the review. All eight studies undertook a cost–utility analysis, presenting results as cost per quality-adjusted life-year (QALY), and all compared deferasirox with DFO. Four studies considered only beta-TM patients, one study considered SCD patients, one study included only myelodysplastic syndrome (MDS) patients and two studies considered beta-TM, SCD and MDS patients all together. Two studies had a UK perspective, three studies had a US perspective and the remaining studies were Canadian, Brazilian and European. The four studies in beta-TM patients adopted a long-term time frame (lifetime/50 years); the remaining studies appeared to be limited to 1 year. All of the studies had industry author affiliations and there was a large degree of overlap, in terms of both data sources and authors, between a number of the studies.

The results of the published economic evaluations were generally consistent and appear to demonstrate the cost-effectiveness of deferasirox compared with DFO for the treatment of iron overload in a number of different patient populations and study locations. However, a number of assumptions and, in the case of the long-term studies, extrapolation from short-term RCT data were required, which render the results highly speculative.

Because of the paucity of long-term data, a simple short-term (1 year) model was developed that assessed the costs and benefits of deferasirox, deferiprone and DFO in beta-TM and SCD patients. The model used an NHS perspective and expressed outcomes in terms of cost per QALY. The only difference between chelators in the short term was assumed to be limited to quality of life. The effects of adverse events and adherence were not considered in the analysis.

Even with this relatively simple model a number of assumptions were required in order to generate results. As such all results should be interpreted as indicative rather than factual. The results of the economic model suggest that deferasirox may be a cost-effective strategy (cost per QALY below £30,000 per year) for beta-TM and SCD patients compared with DFO. However, the cost-effectiveness is highly dependent upon the age of the patient and the use of balloon infusers to administer DFO. If deferasirox is compared with deferiprone it is likely that it will be cost-effective only for young children. Furthermore, if deferiprone is proven to offer the same health benefits as deferasirox, deferasirox will not be cost-effective for any patient compared with deferiprone.

Implications for the NHS

In terms of the financial impact placed upon the NHS by the introduction of deferasirox, our analysis indicates that for both beta-TM and SCD patients the total budget impact is likely to be in the region of £8 million. However, this figure is dependent upon the usage of DFO and deferiprone in current practice. Deferasirox is most economically attractive when compared with DFO administered via a balloon infuser and least attractive when compared with deferiprone.

Conclusions

This review reveals that in the short term there is no evidence available to indicate a clinical difference between any of the three chelators in terms of removing iron from the blood and liver. In terms of cost-effectiveness, deferasirox may be cost-effective compared with DFO in beta-TM and SCD patients but it is unlikely to be cost-effective compared with deferiprone.

Recommendations for future research

Elucidating the long-term benefits of chelation therapy, including issues of adverse events and adherence, should be the primary focus for future research. As an adjunct to this, financial support for research into new strategies for measuring iron overload, such as T2*, appears justified, as do further clinical trials in other patient populations such as those with MDS. All future trials should aim to be consistent and transparent in reporting study design and results, which should aid decision-making when trying to make comparisons across trials. There is also a need for an independent costing study to be undertaken in a variety of patients and treatment centres.

Chapter 1

Assessment aims

The review evaluated the clinical effectiveness and cost-effectiveness of deferasirox in the treatment of iron overload due to red blood cell transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia, such as sickle cell anaemia, beta-thalassaemia major (beta-TM) and myelodysplastic syndrome (MDS).

Comparisons have been made between deferasirox and deferoxamine (DFO), deferiprone or placebo.

To ensure that the wider picture of iron-chelating therapy is considered, comparisons were also made between deferiprone (alone and in combination with DFO) and DFO (alone and in combination with DFO).

Chapter 2
Background

Description of health problem

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

Aetiology, pathology and prognosis

The aetiology, pathology and prognosis of iron overload in transfusion-dependent anaemia is somewhat dependent on the underlying anaemic condition. The most common chronic anaemic conditions that require frequent blood transfusions are beta-TM, sickle cell disease (SCD) and MDS.

Beta-thalassaemia and SCD are recessively inherited anaemias caused by variants of the haemoglobin genes. People who inherit one affected beta-globin gene are healthy carriers (e.g. of beta-thalassaemia, or haemoglobin E, S or C).

People who inherit two beta-thalassaemia genes (or one beta-thalassaemia gene and one haemoglobin E gene) have a serious, usually transfusion-dependent anaemia. Those who need to start regular transfusions before 2 years of age are said to have beta-TM. A minority have a milder disorder not requiring regular transfusions in early life but may become transfusion dependent later: these are said to have beta-thalassaemia intermedia (beta-TI).

Individuals who inherit two genes for haemoglobin S, SS, or one gene for haemoglobin S and one gene for beta-thalassaemia or haemoglobin C, D Punjab or O Arab have a sickle cell disorder.

Beta-thalassaemia major

Newborns with beta-TM have a near total inability to produce beta-globin chains, leading to a deficiency in the production of haemoglobin. By the age of 6 months the child will begin to develop severe anaemia, which, if left untreated, will lead to increased erythropoietin production and expansion of the ineffective bone marrow, bone deformities, growth retardation, hypersplenism and eventually death.

Treatment by regular blood transfusion reverses these pathological mechanisms so that growth and development are normal until around 11 years of age.[3,4] However, with each transfusion, iron is deposited in the body, particularly in the heart, liver and endocrine system.[5] The resulting iron overload causes failure of growth and development at puberty and early death (between 12 and 24 years of age), usually from cardiac complications.[6]

Patients who are given iron chelation therapy have the potential to live into their 40s and beyond.[6] Unfortunately, adherence to treatment is suboptimal, particularly in adolescents and young adults, with as many as one-third of patients non-compliant with treatment.[7] This non-adherence to therapy is thought to be the major contributing factor to deaths in younger patients.[6]

Other beta-thalassaemias

Beta-TI encompasses a broad spectrum of severity ranging from transfusion-independent mild anaemia to a condition that resembles beta-TM.[8] Most patients do not receive frequent blood transfusions in their early years although a majority become transfusion dependent as a result of complications later in life. Even without regular transfusions patients can develop iron overload because of ineffective erythropoiesis and intestinal iron absorption, although this generally occurs later in life.[8]

Haemoglobin E/beta-thalassaemia also has a wide spectrum of severity: about 25% of patients have mild thalassaemia intermedia and rarely develop significant problems or require treatment.[8] Up to

50% have typical thalassaemia intermedia and may develop iron overload as a result of transfusions or increased gastrointestinal (GI) iron absorption.[8] The remainder have thalassaemia major[8] and are at risk of transfusional iron overload from an early age.

Sickle cell disease

SCD is a highly heterogeneous group of disorders in which the red blood cells contain haemoglobin S with little or no normal haemoglobin A and can sickle when they are short of oxygen. The common, severe form is sickle cell anaemia (SS or homozygous haemoglobin S).

By the age of 6–9 months most children with homozygous SCD rapidly develop haemolytic anaemia because of a substantial decrease in the survival of red blood cells (17 days compared with 120 days in healthy people).[9] To partly compensate for the reduced oxygen-carrying capacity, patients often have an increased plasma volume and enlarged heart.

Patients with SCD also develop vaso-occlusion in which the sickled red blood cells block blood vessels in the body leading to 'painful crisis', acute chest syndrome and stroke.[10–12] Painful crisis itself is not life threatening but a recent study indicates that almost 60% of SCD patients who die suddenly of natural causes or within 24 hours of seeking emergency care initially presented with painful crisis.[13] The majority of deaths in homozygous SCD patients are due to infections (48%) or stroke (10%).[13]

In SCD patients, chronic blood transfusions are primarily given to prevent secondary stroke and, more recently, primary stroke.[14] The ideal duration of transfusion therapy is yet to be determined, although at least 3 years has been proposed and possibly lifelong.[15] Chronic transfusion therapies have also been initiated to prevent acute chest syndrome, to reduce the incidence of painful crises, and in chronic heart failure or renal failure in SCD.[14] The ideal transfusion intensity and duration are uncertain.

As with the thalassaemic patients, repeated blood transfusions for SCD can quickly cause iron overload. The pathology of iron overload in SCD patients has not been as widely studied as that in thalassaemia patients but the limited evidence suggests that the pattern of iron-induced organ damage differs in SCD patients compared with thalassaemia patients.[16] SCD patients appear to have less liver disease and endocrine dysfunction than beta-thalassaemia patients.[16] It is also possible that SCD patients may be protected from iron-induced cardiac damage.[16,17] Further research is needed to confirm these findings as the studies thus far have been of small size and have been unable to adequately match participants for age and transfusion burden. As thalassaemia patients typically receive transfusions more frequently and from an earlier age than SCD patients, this may be a confounding factor.

The survival of iron-overloaded SCD patients receiving chelation therapy has not been determined. In view of the evidence that the pattern of iron-induced organ damage may not be the same in SCD as in thalassaemia, it seems conceivable that the survival advantage offered by chelators may also differ depending on the underlying anaemic condition.

Myelodysplastic syndrome

MDS is a heterogeneous group of diseases typified by bone marrow failure and an increased risk of developing myeloid leukaemia. The primary form of MDS generally occurs in patients over 50 years of age; the secondary form can occur at any age and is acquired from bone marrow damage following chemotherapy or radiotherapy.

There are two classification systems for MDS: the International Prognostic Scoring System (IPSS) and the World Health Organization (WHO) classification system. These are used to indicate a patient's risk of developing acute myeloid leukaemia. According to the IPSS, patients are classified as being at low, intermediate-1, intermediate-2 or high risk of developing acute myeloid leukaemia, with median survivals of 5.7, 3.5, 1.2 and 0.4 years respectively.[18]

The WHO classification for MDS patients is split into eight categories: RA, RARS, RCMD, RCMD-RS, RAEB-1, RAEB-2, MDS del (5q) and MDS-U.[19] There is no simple relationship between the IPSS and the WHO systems, although patients at low and intermediate-1 risk (IPSS) fall into the following WHO subgroups: RA, RARS, RCMD, RCMD-RS and MDS del (5q).[20] Nonetheless, a number of patients at low and intermediate-1 risk can be found in the remaining WHO subgroups.[20] See Appendix 1 for the WHO classification system.

Patients with MDS frequently have transfusion-dependent anaemia and after receiving more than 20 units of red blood cells risk developing iron

overload.[20] There are few data on the pattern of iron-induced organ damage in MDS patients or on the benefits of chelation therapy although a recent small study indicated that there may be potential survival benefits to treating this patient population.[21]

Other rare anaemias

There are a number of rare anaemic conditions that may require frequent blood transfusions, such as Diamond Blackfan anaemia (DBA) and aplastic anaemia.

DBA is a rare heterogeneous congenital bone marrow failure disorder characterised by low red blood cells and the development of anaemia, typically within the first 2 years of life.[22] The majority of patients can be managed by steroids but some patients require frequent blood transfusions either in combination with steroids or alone, which can lead to iron overload.[22]

Aplastic anaemia is a rare disorder caused by bone marrow failure; aplastic anaemia usually refers to the acquired form of the condition although there are a number of inherited forms such as Fanconi anaemia. The acquired form generally occurs as the result of an autoimmune reaction, typically idiopathically (no known cause).[23] The majority of patients will require frequent blood transfusions at some time in their life (potentially lifelong) and are hence at risk of iron overload.

Epidemiology

Evidence on the incidence and prevalence of iron overload in the UK is not currently available. Indirect estimates can be produced by calculating the size of the population undergoing frequent blood transfusions and hence at risk of iron overload. The population size will vary depending on the underlying anaemic condition. As discussed earlier, the most common conditions requiring frequent blood transfusions are beta-TM, SCD and MDS.

Beta-thalassaemia major

The most reliable and up-to-date estimates of the number of beta-TM patients in the UK are thought to be held in the UK Thalassaemia Register. The register contains data such as date of birth, ethnicity, UK region of origin, deaths and cause of death. The database was thought to be 97% complete but unfortunately became inactive at the end of 2003. For the purpose of this HTA report the authors were granted access to an anonymised copy of the register. The database has information on 850 patients diagnosed with beta-TM, of whom 696 were alive in 2003. In general, the majority of beta-TM patients in the UK are of Indian, Pakistani or Mediterranean origin (see *Figure 1*). There is wide geographic variance in the distribution of beta-TM in the UK, with the majority of patients residing in the south of England (see *Figure 2*). However, clinical experts indicate that most affected births now occur in the Midlands and the north.

Of the 696 beta-TM patients alive in 2003, 72 had undergone bone marrow transplantation and thus were not considered to be undergoing chronic blood transfusions. The remaining 624 patients were assumed to be receiving chronic transfusions and hence to be at risk of suffering from iron overload. The Office for National Statistics estimated the UK population to be 59,533,800 in mid 2003.[24] Using these figures we estimate the prevalence of iron overload in beta-TM patients to be approximately 1 per 100,000 population in the UK. However, as shown by *Figures 1* and *2*, the prevalence of iron-overloaded beta-TM patients in the UK will vary significantly depending on the geographic location and the presence of certain ethnic groups.

The incidence of iron-overloaded beta-TM patients is a factor of both the number of affected individuals migrating to the UK and the number of affected births, which in turn is dependent on the uptake of screening programmes. There may be a lag between the date of birth and the diagnosis of beta-TM, and similarly between the diagnosis of beta-TM and the development of iron overload. However, for our purposes we will assume that the annual number of births reported to the UK Thalassaemia Register approximately equates to the incidence of beta-TM.

The UK Thalassaemia Register did not have any patients listed as being born in 2003. This is to be expected as patients are rarely diagnosed at birth. To calculate the incidence of iron-overloaded beta-TM patients in 2003, the number of patients born in each year between 1990 and 2003 (see *Figure 3*) was estimated. Taking the mean gives an incidence of 15 iron-overloaded beta-TM patients per year. Using 2003 UK population figures (59,533,800) this gives an incidence rate of 0.03 iron-overloaded beta-TM patients per 100,000 population in the UK.

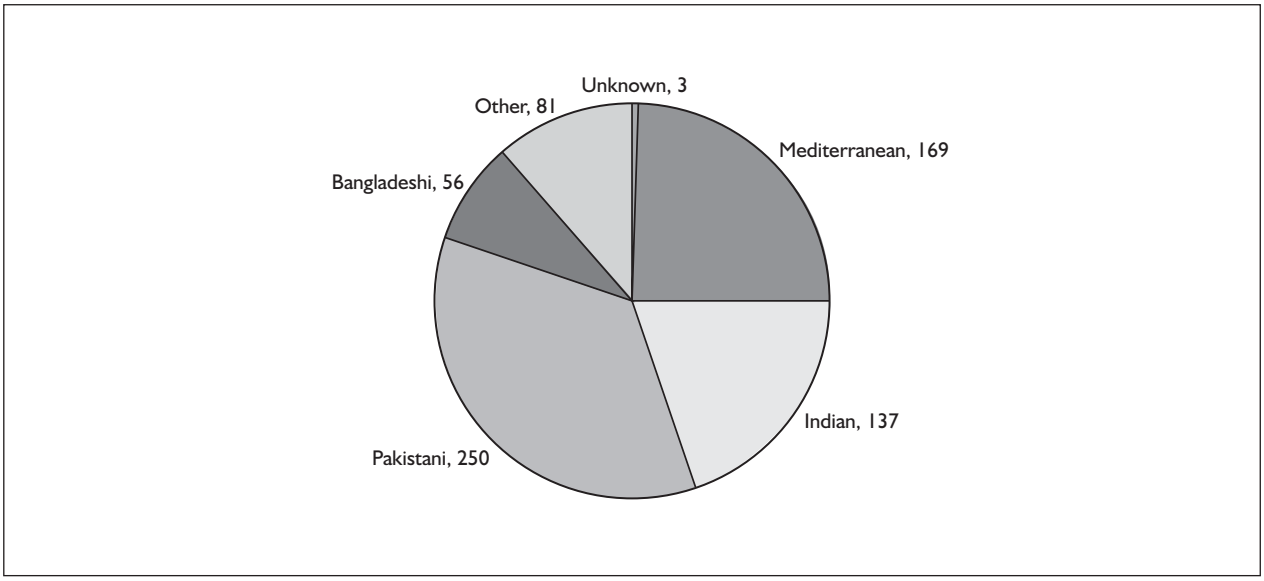

FIGURE 1 *Distribution of beta-thalassaemia major in the UK by ethnicity.*

Other beta-thalassaemias

Analysis of the UK Thalassaemia Register indicates that in 2003 there were 99 beta-TI patients and 63 haemoglobin E/beta-thalassaemia patients who had not had a bone marrow transplant. Only a small proportion of these are likely to be at risk of iron overload.

Sickle cell disease

Approximately 12,500 individuals are estimated to be living with SCD in the UK, and in the region of 318 infants are born with SCD annually in England (Allison Streetly, Sickle Cell and Thalassaemia Screening Programme, October 2007, personal communication). Approximately 5% of SCD patients receive chronic transfusions.[14] Applying this figure to the population of SCD patients in the UK (12,500) gives a prevalence of approximately 625 chronically transfused patients potentially suffering from iron overload. The incidence of iron-overloaded SCD patients in the UK can be calculated in a similar way (i.e. applying 5% to 318 infants born each year) and is estimated to be approximately 16 infants annually.

Using 2003 UK population figures (59,533,800) gives a prevalence rate of 1.04 and an incidence rate of 0.02 iron-overloaded SCD patients per

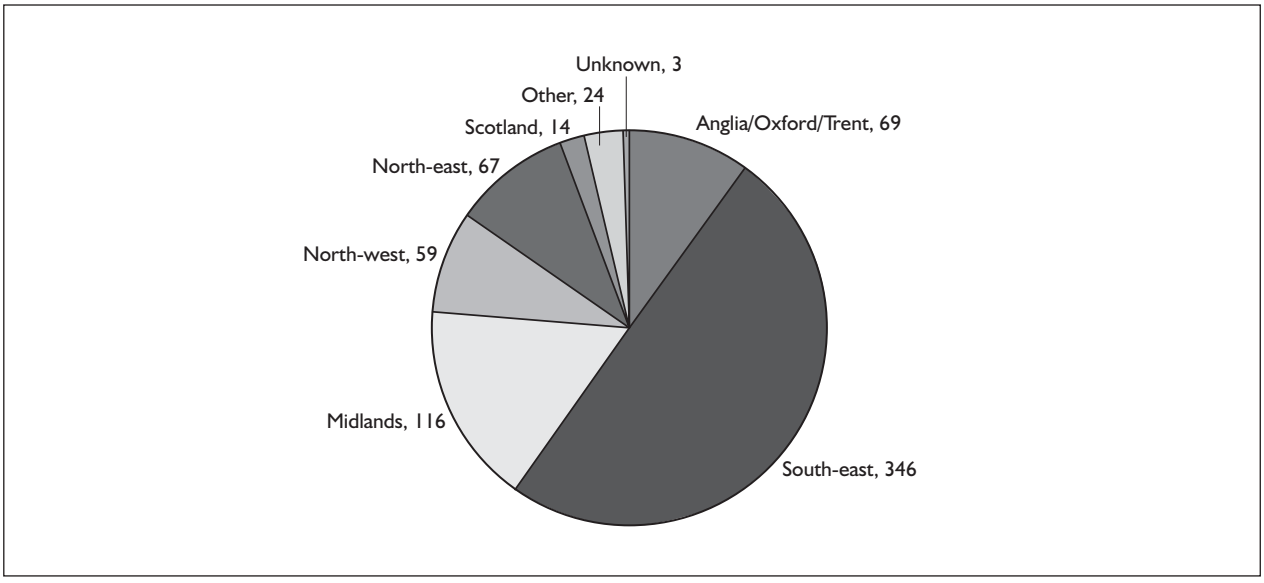

FIGURE 2 *Geographic location of beta-thalassaemia major patients in the UK.*

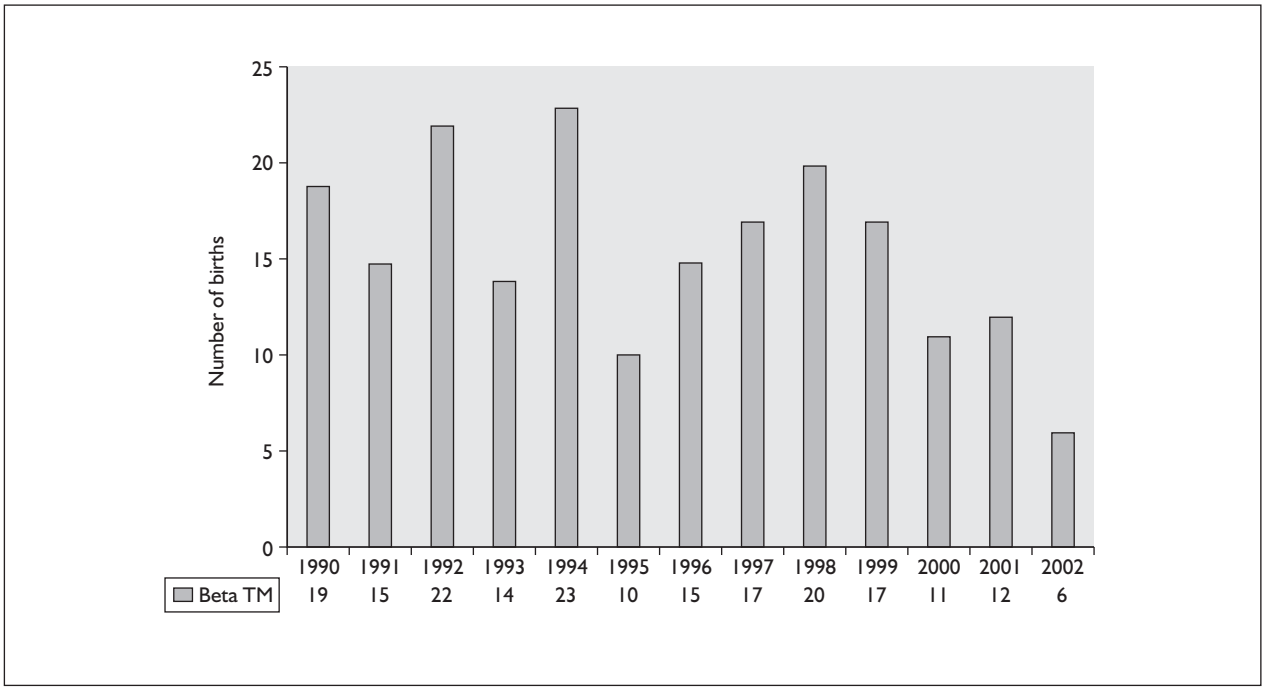

FIGURE 3 *Estimation of the birth rate of beta-thalassaemia major patients.*

100,000 population in the UK. However, given recent evidence that transfusions can help prevent primary stroke in high-risk children[25] it is likely that the prevalence and incidence rates may increase.

SCD is primarily found in black ethnicities (predominantly from sub-Saharan Africa). As such there is a very unequal geographic distribution of SCD in the UK, with the highest density being located in inner city areas with a high proportion of ethnic minority populations.[26]

Myelodysplastic syndrome

Epidemiological data on MDS are sparse. There are no estimates of the prevalence of MDS. Several studies, both in the UK and elsewhere, have attempted to estimate the incidence of MDS and report rates ranging from 1 to 12.6 per 100,000 population.[27–38] The estimates were generally higher for the UK ranging from 3.6 (England and Wales only) to 12.6 per 100,000.[28,31,33,35] Using UK 2003 population estimates (59,533,800) this equates to an annual incidence of MDS in the UK of approximately 2143–7501. However, not all MDS patients require chronic transfusions and not all transfusion-dependent MDS patients are at risk of iron overload.

One study[20] based on the WHO classification scheme ascertained that only RA/RARS patients receiving chronic blood transfusions are at risk of iron-induced morbidity and mortality, because of their prolonged survival. RA/RARs patients accounted for approximately 23% (110/467) of all MDS patients in the study. Approximately 10% of the total (48/467) were also transfusion dependent and therefore at risk of iron overload. Hence, the incidence of MDS patients requiring transfusions and at risk of iron overload can be estimated as approximately 0.36–1.26 per 100,000 population. Using 2003 UK population figures (59,533,800) this gives an incidence of approximately 214–750 iron-overloaded MDS patients per year in the UK.

As there was no estimate of the prevalence of iron overload in MDS patients, we attempted to calculate a rough estimate using the incidence rate and the median survival. Ideally mean survival would be used because survival distributions tend to be skewed, but when mean data are not available the median can provide a rough estimate. Malcovati *et al.*[20] calculated the median survival in RA/RARS as approximately 9 years (108 months). Given an incidence of 214–750 cases per year and a survival of 9 years this gives a prevalence of 1924–6750 patients in the UK (prevalence rate of 3.2–11.3 per 100,000 population).

Other rare anaemias

The prevalence and incidence of iron overload in other anaemic conditions is difficult to estimate because of the rarity of the conditions and/or the spectrum of transfusional requirements; however, numbers are likely to be extremely small. For example, estimates of DBA indicate that there are in the region of 125 patients in the UK,[22] not all of whom will be suffering from iron overload.

Impact of health problem

Iron overload caused by frequent blood transfusions is associated with increased morbidity and mortality. The majority of evidence is derived from studies of beta-TM patients, in which the link between iron overload and reduced survival has been most clearly documented.[6] Patients with beta-TM and iron overload have increased cardiac complications, which have a major bearing upon mortality.[5] The effects of iron overload in SCD and MDS patients have been less widely studied. As with beta-TM patients, SCD patients are often young when transfusions are initiated. However, SCD is a very different condition and transfusions are not often continued lifelong, so the potential for iron overload may be less than in beta-TM patients. Similarly, the potential for MDS patients to accumulate iron may be limited as these patients are generally older and may not survive long enough to accumulate iron to toxic levels. Nevertheless, regardless of the underlying anaemic condition, the burden of iron overload in those patients who receive frequent blood transfusions for a prolonged period of time is likely to be considerable. However, because of the rarity of the condition, the financial impact upon the NHS is unlikely to be great. It is worth noting that the financial impact is likely to vary across primary care trusts (PCTs) because of the unequal geographic distribution of disorders, particularly with regards to beta-TM and SCD.

Measurement of iron overload

Liver iron concentration (LIC) is generally considered the reference standard for estimating iron burden.[8] This is typically measured from liver biopsy samples but may also be measured using superconducting quantum interference devices (SQUID) or magnetic resonance imaging (MRI), both of which are non-invasive but which may not be available in all centres. All of these measures are subject to variability because of a lack of standardisation of methodology; furthermore, estimates of LIC via biopsy may not equate with SQUID or MRI measures (personal communication with clinicians).

The target for liver iron levels is below 7 mg/g dry weight (dw).[8] Levels above 15 mg/g have been associated with a high risk of cardiac death in thalassaemia patients.[3,4] However, levels below 1 mg/g are evidence of overchelation, which is also undesirable.

In clinical practice, serum ferritin monitoring is more commonly used to assess the total body iron burden and monitor the patient's response to treatment, as liver biopsies carry a morbidity and mortality risk.[39] Serum ferritin testing is well established and easy to perform, although single measurements may not be as reliable as LIC.[8,40] However, a long-term profile should be indicative of the overall trend in body iron stores. Maintaining a ferritin level of approximately 1000 µg/l or less has been recommended in thalassaemia and SCD patients.[8,40]

A recent extension of the use of MRI is in the assessment of cardiac iron burden, a technique known as T2* cardiac magnetic resonance imaging (CMR). This method is of particular value in thalassaemia patients, for whom iron-induced cardiac dysfunction is the leading cause of morbidity and mortality.[6] This method has not been directly calibrated against myocardial iron content but is widely acknowledged as useful for detecting cardiac iron overload.[41] A recent study estimated that severe iron overload in the heart was present when T2* was < 10 ms.[42] Considering that iron-induced cardiac damage is reversible with intensive chelation therapy if treatment is initiated early enough, timely detection is crucial.[43] The general consensus is that myocardial iron cannot be predicted from LIC or serum ferritin and that conventional measurements of cardiac function only detect those with advanced disease.[41] It is therefore likely that this method will increasingly be used, particularly in thalassaemia patients and/or patients at risk of cardiac complications.

Current service provision

Current treatments for iron overload

The conventional treatment for transfusional haemosiderosis is chelation therapy aimed at reducing iron stores or maintaining an iron balance. Treatment with iron chelators is primarily governed by the degree of iron overload and the

transfusional requirements of patients. The risk of iron overload increases once patients have received approximately 20 transfusions.

Currently in the UK, patients presenting with transfusional haemosiderosis are treated with DFO. Thalassaemia patients (over the age of 6 years) who cannot tolerate DFO have the option to try deferiprone.[44] There is also growing off-licence usage of DFO in combination with deferiprone in thalassaemia patients following recent reports of their synergistic effects, particularly with regard to cardiac iron levels.[45,46]

According to the licensed indications thalassaemia patients younger than 6 years and other transfusion-dependent anaemic patients (such as those with SCD and MDS) do not have the option to switch to deferiprone.[44] Discussions with clinicians indicate that deferiprone has been used off licence in younger thalassaemia patients and in thalassaemia intermedia, SCD and MDS patients. There is, however, little evidence in the literature on the efficacy and safety of deferiprone in these patient populations.

Deferoxamine

DFO (Desferal®; Novartis) is a large molecule that binds iron in a 1:1 ratio and is subsequently excreted in the urine and faeces. It is available for treating iron overload in patients suffering from beta-TM, SCD and MDS, as well as other transfusion-dependent anaemias and iron-loading conditions. The major drawback of DFO is that its short half-life and the fact that it cannot be absorbed from the intestine necessitates that treatment is given as a subcutaneous infusion over 8–12 hours, five to seven times per week. The dose varies depending on the degree of iron overload and the age of the patient. For established overload the dose is usually between 20 and 50 mg/kg daily.[47]

DFO can be administered in a number of ways but the two most common methods are via the traditional pump or via disposable balloon infusers. The traditional pump is relatively inexpensive but is noisy and cumbersome and also necessitates that patients mix their doses of DFO. The balloon infuser is much more expensive but is smaller and quieter and comes with premixed doses of DFO. As such it is thought to assist with patient compliance as it reduces the patient burden and facilitates normal daily activities.

The most commonly reported side effects are injection site reactions (≥ 1/10), arthralgia/myalgia (≥ 1/10), headache (≥ 1/100 to < 1/10), urticaria (≥ 1/100 to < 1/10), nausea (≥ 1/100 to < 1/10) and pyrexia (≥ 1/100 to < 1/10).[48]

Ocular and auditory disturbances have been reported following prolonged therapy. It is therefore recommended that auditory and ocular tests be carried out before long-term therapy and at 3-monthly intervals thereafter.[48] Growth retardation has also been linked with excessive doses of DFO, hence 3-monthly checks of weight and height are recommended in children.[48]

Deferiprone

Deferiprone (Ferriprox®; Swedish Orphan) is an oral iron chelator that binds iron in a 3:1 ratio and is subsequently excreted primarily in the urine. Its European licence limits its use to thalassaemia patients over the age of 6 years in whom DFO is contraindicated or is not tolerated.[44] For adults and children over 6 years of age it is given at a dose of 25 mg/kg three times daily (maximum dose 100 mg/kg daily).[47]

The most commonly reported side effects are nausea (≥ 1/10), abdominal pain (≥ 1/10), vomiting (≥ 1/10), arthralgia (≥ 1/100 to < 1/10), increased alanine aminotransferase (ALT) (≥ 1/100 to < 1/10), neutropenia (≥ 1/100 to < 1/10), increased appetite (≥ 1/100 to < 1/10) and agranulocytosis (1/100).[49]

Because of the risk of neutropenia and agranulocytosis, deferiprone is contraindicated in patients with a history of recurrent episodes of neutropenia or a single episode of agranulocytosis.[49] Weekly neutrophil counts are recommended for all patients receiving deferiprone; in the case of neutropenia, rechallenge is not recommended; in the case of agranulocytosis, rechallenge is contraindicated.[49]

There have been no studies in patients with hepatic or renal impairment; in these patients hepatic or renal function should be monitored regularly.[49] Special care must also be taken in patients with hepatitis C; careful monitoring of liver histology is recommended.[49]

Guidelines

Because of the relative rarity of iron overload there are no national service frameworks nor any national (UK) guidelines on how to treat patients with this condition. There are, however, a number of disease-specific guidelines, which are not necessarily restricted to the UK.

Thalassaemia

As an adjunct to the Thalassaemia International Federation *Guidelines for the clinical management of thalassaemia*,[8] the UK Thalassaemia Society produced the *Standards for the clinical care of children and adults with thalassaemia in the UK*.[50] These guidelines state that subcutaneous DFO therapy should be initiated after transfusion-dependent children receive 10–12 transfusions or when the serum ferritin level is consistently greater than 1000 µg/l. Deferiprone therapy, in combination with DFO or alone, should be restricted to patients with high iron levels after first attempting to improve adherence with DFO.[50] It is worth noting that both of these guidelines were issued before deferasirox was generally available. Individual centres typically have their own guidelines that are more up to date.

Sickle cell disease

The National Heart Lung and Blood Institute guidelines[40] recommend initiation of chelation therapy once liver iron stores reach 7 mg/g dw or when cumulative transfusions reach approximately 120 cc of packed red blood cells per kilogram of body weight. They also state that serum ferritin levels above 1000 µg/l may be used as an indicator but stress that there is a risk of under- or overtreatment because of the unreliability of this measure in SCD patients.

Myelodysplastic syndrome

The British Society for Haematology[51] recommends iron chelation therapy for patients who have received approximately 25 units of red cells and for whom long-term transfusion therapy is likely, such as patients with MDS del (5q). Target serum ferritin levels of < 1000 µg/l are recommended. At the time of issuing guidance (2003) only DFO was advocated; because of a lack of data deferiprone was not recommended. No guidance on deferasirox was issued as the agent was not yet available.

Current service costs

The cost of treating iron overload depends on the perspective taken; from an NHS perspective only the direct health-care costs are considered. These costs comprise the cost of the iron chelator together with any administration (delivery and equipment) and monitoring costs.

Using prices from the *British National Formulary* (BNF) 53[47] for an average 70-kg adult the drug costs of DFO can be estimated to range from £3323 per year (10 mg/kg dose) to £7756 per year (50 mg/kg dose), assuming treatment is required 5 days per week (see). However, in addition to this are the costs of delivery and equipment together with monitoring costs.

The drug costs of deferiprone for an average 70-kg adult receiving 25 mg/kg are approximately £5848 per year (see *Table 2*). There are no administration costs although a number of monitoring tests are required, including regular neutrophil counts; these should be included in the costing of deferiprone.

Deferasirox

Deferasirox (Exjade®; Novartis) is an orally active iron-chelating agent that binds iron in a 2:1 ratio and is primarily excreted in faeces. It is given once daily as an oral suspension (usually in water or fruit juice) at a dose of 10–30 mg/kg.[47]

Deferasirox may be of particular value in treating patients with iron overload who cannot

TABLE 1 *Costs of deferoxamine (DFO), 20–50 mg five times weekly for a 70-kg adult*

Dose	20 mg/kg	30 mg/kg	40 mg/kg	50 mg/kg
Required daily dose	1400 mg	2100 mg	2800 mg	3500 mg
Number 500 mg vials	3	0	2	3
Number of 2 g vials	0	1	1	1
Cost per day	£12.78	£17.05	£25.57	£29.83
Cost per year	£3323	£4433	£6648	£7756

Assumes no vial sharing. Prices are based on generic formulation of desferrioxamine mesilate. All prices are based on the March 2007 edition of the *British national formulary*.[47] Available formulations are 500-mg vial priced at £4.26; 2-g vial priced at £17.05.

TABLE 2 *Costs of deferiprone, 25 mg/kg three times daily for a 70-kg adult*

Required daily dose	**5250 mg**
Number of tablets per day	10.5
Cost per day	£16.02
Cost per year	£5848

All prices are based on the March 2007 edition of the *British national formulary*.[47] Available formulation is 500 mg, 100-tablet pack priced at £152.39.

tolerate DFO and who are not suitable for, or who are intolerant of, deferiprone. The ease of administration of deferasirox (oral) compared with DFO (infusional) might improve patient adherence to therapy[7] and, if effective, may also improve quality and quantity of life.

Licensed indication

The approved licensed indication in Europe[52] is:

- the treatment of chronic iron overload due to frequent blood transfusions (≥ 7 ml/kg/month of packed red blood cells) in patients with beta-TM aged 6 years and older
- the treatment of chronic iron overload due to blood transfusions when DFO therapy is contraindicated or inadequate in the following patient groups: patients with other anaemias, patients aged 2–5 years, patients with beta-TM with iron overload due to infrequent blood transfusions (< 7 ml/kg/month of packed red blood cells).

Adverse effects and contraindications

The most common side effects reported are increased serum creatinine (≥ 1/10), headache (≥ 1/100 to < 1/10), GI disorders including diarrhoea, constipation, nausea, vomiting and abdominal pain (≥ 1/100 to < 1/10), increased ALT (≥ 1/100 to < 1/10), proteinuria (≥ 1/100 to < 1/10) and rash (≥ 1/100 to < 1/10).[53]

Deferasirox is not recommended in patients with severe hepatic impairment as safety tests have not been performed in this population.[53] Liver function test elevations have been observed in studies, hence monthly liver function tests are recommended.[53]

Deferasirox is contraindicated in patients with an estimated creatinine clearance of less than 60 ml/minute.[53] Because of the risk of renal dysfunction, regular creatinine monitoring is recommended as follows: in duplicate before treatment; weekly for the first month of treatment; and then monthly thereafter.[53] Proteinuria tests should also be performed monthly, and additional markers of renal tubular function measured as needed.[53]

Auditory and ocular disturbances have been reported. Hence, hearing and eye tests are recommended before treatment and every 12 months thereafter.[53] As a precautionary measure, growth and sexual development should also be monitored annually in children.[53] Cardiac dysfunction should also be measured regularly in individuals with severe iron overload.[53]

TABLE 3 *Costs of deferasirox, 10–30 mg once daily for a 70-kg adult*

Dose	**10 mg/kg**	**20 mg/kg**	**30 mg/kg**
Required daily dose	700 mg	1400 mg	2100 mg
Number of tablets	1 x 500 mg; 1 x 250 mg	2 x 500 mg; 1 x 250 mg; 1 x 125 mg	4 x 500 mg; 1 x 125 mg
Cost per day	£25.20	£46.20	£71.40
Cost per year	£9198	£16,863	£26,061

All prices are based on the March 2007 edition of the *British national formulary*.[47] Available formulations are 500 mg, 28-tablet pack priced at £470.40; 250 mg, 28-tablet pack priced at £235.20; 125 mg, 28-tablet pack priced at £117.60.

Cost of deferasirox

The drug costs of deferasirox comprise the cost of the drug itself together with the costs of monitoring. The annual costs of deferasirox in an average 70-kg adult can be estimated to range from £9198 (10 mg/kg dose) to £26,061 (30 mg/kg dose). The costs of monitoring will be similar to those for other iron chelators with the addition of regular creatinine monitoring tests (see *Table 3*).

Subgroups

Differentiation between adult and paediatric patients appears to be clinically important as children tend to metabolise deferasirox more rapidly than adults.[54] Patients with different anaemic conditions may also not respond in the same way, as the pattern of iron-induced damage may differ between anaemic conditions.

Guidelines for the usage of deferasirox

There are currently no national guidelines for the use of deferasirox. Comprehensive local guidelines have been developed by Paul Telfer for the use of deferasirox for iron chelation therapy in transfusion-dependent patients managed in the East London and Essex Clinical Haemoglobinopathy Network. A copy of these guidelines is presented in Appendix 2.

Current usage of deferasirox in the NHS

The current usage of deferasirox in the NHS is unknown. Analysis of the 2004 UK Thalassaemia Society patient questionnaire indicates that usage is very low and mainly limited to clinical trials. Contact with clinical experts confirms that deferasirox usage is currently low (estimated to be used in less than 5% of transfusion-dependent patients in the UK), with considerable geographic variability depending on the PCT policy and availability of funding.

We contacted Novartis to obtain more recent and accurate estimates of deferasirox usage in the UK but Novartis felt unable to release this information as it was deemed proprietary (Novartis, July 2007, personal communication).

Previous reviews of effectiveness

Seven published systematic reviews were identified by our search strategy. All of the reviews attempted to address the role of iron chelation therapy for iron overload, of which four also included a meta-analysis (see Appendix 3).

The review by Addis *et al.*[55] was limited to deferiprone only, with no consideration of comparators. This review was carried out when the use of deferiprone was still relatively rare and consequently the number of patients included in the studies is small and limited to cohort studies. Based on findings from fewer than 100 patients it reported that half of all patients given a dose of deferiprone of 75 mg/kg or more achieved negative iron balance and three-quarters of patients reduced their levels of serum ferritin, on average by almost one-quarter. This review concluded that deferiprone has clinical efficacy in achieving negative iron balance and reducing body iron burden in highly iron-overloaded patients.

The Addis *et al*.[55] review was subsequently included in the far broader review undertaken by the Malaysian Health Technology Assessment Unit,[56] which, in addition to chelation therapy, considered other aspects of thalassaemia management such as screening, transplantation and bone marrow treatment. In terms of chelation therapy it presented evidence from studies showing beneficial impacts of DFO in terms of a wide range of factors including endocrine function and growth, cardiac disease, liver disease, survival, quality of life and cost effectiveness; and of deferiprone in terms of safety, increasing urinary iron excretion, decreasing serum ferritin levels and reducing liver iron. However, in all instances, the number of studies cited to support the evidence was small (and many of the studies that were listed as included in the review in the appendix were not referred to in the text, including the review by Addis *et al*.[55]). Nevertheless, it was concluded that there was sufficient evidence to conclude that both DFO and deferiprone are effective in preventing or improving serious complications of the disease.

The review by Caro *et al*.[57] was the first to include studies that directly compared one iron chelator with another. Most of the studies included were case series and clinical trials, with only one randomised controlled trial (RCT). The findings from this review suggested that DFO was more effective than deferiprone in reducing LIC. It should however be noted that, in general, baseline LIC values were greater in patients receiving DFO, which could arguably bias in favour of DFO in terms of the chances of being able to achieve a greater reduction in LIC. Thus, to account for these differences, an analysis of covariance (ANCOVA) was conducted controlling for LIC at

baseline, but this did not affect the results. Other potential sources of bias were also noted in the review. First, deferiprone patients had often failed DFO in the past (including for non-adherence) and so may also have been more prone to fail on deferiprone (for similar reasons). Second, deferiprone doses were generally low compared with DFO doses. Finally, LIC was only one of a number of outcomes included and often only in a small subset of study patients (generally a subset of those who continued treatment for a prolonged period of time and for whom long-term information on changes in iron load was available). Therefore, as the authors concede, the 'methodological caveats and the heterogeneity of study characteristics' raise questions about the appropriateness of pooling the data.

A larger and more up-to-date review was carried out in 2004 by Franchini and Veneri,[58] which primarily focused on deferiprone and combination therapy but also considered subcutaneous bolus DFO injections and two initial phase I RCTs of deferasirox.[59,60] The meta-analysis of non-comparative studies indicated that deferiprone was effective in reducing levels of serum ferritin (overall mean reduction of around 25%), which in some studies was maintained for 3–4 years. A number of adverse events were commonly reported (GI symptoms, arthropathy, neutropenia, agranulocytosis and hepatoxicity) although only in a few cases (8.7%) did these necessitate permanent discontinuation of the drug. It was therefore concluded that deferiprone was a safe and effective oral chelator but that further studies were required to evaluate the impact on cardiac and liver disease. The authors also recommended long-term follow-up studies of bolus DFO injections because of safety concerns. With regards to deferasirox the authors concluded that the results of the phase I trials were promising in terms of safety and efficacy but that more studies were required.

The 2005 Cochrane review by Roberts *et al.*[61] included a comparison of different iron chelators. This was the only identified review that exclusively included RCTs. However, it was found that very few trials measured the same outcomes, which limited the ability of the review to conduct meta-analysis. Based on the outcomes that were available, the study findings did not suggest that any one chelator was better than the other and so it was concluded by the authors that there was no evidence to change current practice.

The 2006 review by VanOrden and Hagemann[7] focused on deferasirox. Despite stating that this review was confined to evidence in phase III trials, the review includes evidence from phase I and phase II trials as well as pharmacokinetic studies in both humans and non-humans. Three-quarters of the patients in the efficacy analysis are from a single phase III RCT.[62] No attempt was made to pool the data from the trials and so the findings are presented narratively. The authors conclude that the results presented in the review suggest that deferasirox is as safe and effective as DFO. However, most of the patients included in this review had thalassaemia (and all of the patients in the single phase III trial had this disease) and so further studies are needed to assess the use of deferasirox in patients with other diseases such as SCD and MDS.

Finally, Abetz *et al.*[63] considered the impact of iron overload and its treatment on patients' quality of life. This was concerned entirely with DFO, although it is noted that all of the included studies focused on the impacts of disease on quality of life rather than the impacts of iron chelation in particular. Nevertheless, it was reported that the degree of discomfort associated with DFO treatment was a strong predictor of a negative perception of quality of life. The authors of this review concluded that an oral iron chelator that is at least as efficacious and well tolerated as DFO is needed to improve quality of life, increase adherence and ultimately reduce morbidity and mortality due to iron overload.

During the conduct of this HTA review another review[64] was published in July 2007 comparing the effects of deferiprone versus DFO and combination therapy (deferiprone and DFO) versus DFO or deferiprone. As in the 2005 Cochrane review[61] this second review for the Cochrane Collaboration only included RCTs. Because of the different outcomes used as well as difficulties in assessing baseline characteristics of the included trials the reviewers only pooled data for mean changes in serum ferritin for deferiprone versus DFO. As before, no evidence was found to suggest that any one chelator was better than the other and thus the same conclusion was reached that there was no evidence to suggest change to current clinical practice, i.e. deferiprone is indicated for treating iron overload in people with thalassaemia when DFO is contraindicated or inadequate.

Chapter 3
Methods

A systematic review and economic evaluation were conducted to assess the clinical effectiveness and cost-effectiveness of deferasirox for the treatment of iron overload associated with transfusion-dependent anaemia. The systematic review was guided by the general principles recommended in the QUOROM statement.[65]

To ensure that adequate clinical input was obtained an advisory panel comprising clinicians and experts in the field was established. The role of this panel was to comment on the draft report and answer specific clinical questions as the review progressed.

Identification of evidence: clinical effectiveness

Search strategy

The search incorporated a number of strategies, combining index terms (for the disease) and free text words for the technologies involved (generic and trade names of the drugs). The search strategies had no language restrictions and did not include methodological filters that would limit results to a specific study design. Details of the search strategies and the number of records retrieved for each search are provided in Appendix 4. All references were exported to an EndNote bibliographic database.

The following electronic databases were searched (YD) for relevant published literature for the period 1950 to March 2007:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- DARE (Database of Abstracts of Reviews of Effectiveness)
- EMBASE
- Health Technology Assessment database
- ISI Web of Science – Proceedings (Index to Scientific and Technical Proceedings)
- ISI Web of Science – Science Citation Index Expanded
- MEDLINE
- NHS EED (NHS Economic Evaluation Database).

Hand searching of haematology conference abstracts was conducted for:

- American Society of Hematology 2003–2006
- Aplastic Anaemia and MDS International Federation 2005
- British Society of Haematology 2003–2004
- European Haematology Association 2001–2006.

In addition, publicly available licensing information from the Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA) was obtained for all three agents and used to supplement the published trial literature as appropriate.

In cases in which publications of the trials identified by the search did not include all of the information important to this review, attempts were made to contact authors.

Selection of evidence

The records identified in the electronic searches were assessed for inclusion in two stages.

Two reviewers (CM with either JG or NF) independently scanned all titles and abstracts identified in the search to identify reports that might be relevant to the clinical review. Full text versions of all records selected during the initial screening process were obtained to permit more detailed assessment. These were assessed independently by at least two reviewers (CM, JG, NF) using the inclusion and exclusion criteria shown in *Table 4*. The inclusion/exclusion assessment of each reviewer was recorded on a pretested standardised form. Disagreements were resolved by discussion, and if necessary another reviewer was consulted. Kappa values were calculated for each pairing of reviewers and ranged from 0.7 to 0.9 indicating a high degree of concordance between reviewers. A flow diagram summarising the selection and inclusion of studies is provided in Appendix 5.

Data abstraction

Data extraction for the review of clinical effectiveness was carried out by three reviewers (JG, JK, NF). Data were abstracted by one reviewer and then checked for accuracy by a second reviewer.

Data presented from multiple reports of single trials were extracted as a single record.

Quality assessment

Three reviewers (JG, NF, YD) independently evaluated the included studies for methodological quality using criteria based on the Centre for Reviews and Dissemination Report No. 4.[66] Any discrepancies in quality grading were resolved through discussion.

Data synthesis

Individual study data and quality assessment are summarised in structured tables and as a narrative description.

The primary treatment outcomes relevant to this study were LIC and serum ferritin presented on a continuous scale (means and standard deviations).

The continuous data were summarised in terms of difference in means, providing skewness was not too great. For end-of-study results, continuous data were classed as being skewed if the standard deviation was over half the size of the mean (this is only true if the data can take positive values only; it does not apply to change data for example). Skewed data were not pooled and the results were presented in additional tables, with no statistical analyses performed on these data. When this was the case we contacted the study authors to obtain the change from baseline data that could be included in the analyses. Change in baseline data were reported as end result minus baseline result.

We aimed to conduct meta-analyses for deferasirox versus placebo, deferasirox versus DFO, deferiprone versus DFO and combination therapy (deferiprone and DFO) versus DFO or deferiprone.

RCTs that were deemed suitable for meta-analysis were analysed using Review Manager 4.2. Once the results of each study were summarised using an effect measure, an average value of the effect was computed across studies using either a fixed-effects model if there was little statistical heterogeneity or a DerSimonian and Laird random-effects model[67] when there was unexplained heterogeneity between trial results. Statistical heterogeneity was tested using a standard chi-squared test, with a threshold value of $p < 0.1$, and with the I^2 statistic.[68] If heterogeneity was indicated then further attempts were made to investigate potentially influential study characteristics via suitable subgroup analyses (a priori planned for age and disease). It was acknowledged that certain subgroup analyses might not be possible because of the limited number of studies or insufficient data being available.

If clinical heterogeneity was too great or methodological quality too poor, studies would not be pooled in the meta-analysis. For example, because of suspected clinical heterogeneity, the three methods for measuring LIC (liver biopsy, SQUID and the combination method) were kept separate in the analyses.

Identification of evidence: cost-effectiveness

Search strategy

A comprehensive review of the literature was undertaken to identify all published economic evaluations of chelation therapy for iron overload in chronically transfused patients using the main search strategy outlined in the section on identification of clinical effectiveness evidence.

Selection of evidence

During the clinical effectiveness screening, all papers that appeared to include economic data were selected. Full text copies of these papers were subsequently obtained and two reviewers (CM, ABol) independently assessed them for inclusion, using the economic inclusion and exclusion criteria described in *Table 4*. Any disagreements for inclusion of economic studies were resolved by discussion.

Data abstraction

Data from the included economics studies were abstracted into structured tables by one reviewer (CM) and then checked for accuracy by a second reviewer (ABol).

Quality assessment

Two reviewers (CM, ABol) independently evaluated the included economics studies for methodological quality using criteria based on the critical appraisal checklist for economic evaluations proposed by

TABLE 4 *Inclusion and exclusion criteria*

Study design	Randomised controlled trials (RCTs)
	Economic evaluation
Patient population	Patients with chronic anaemia requiring regular blood transfusions
Interventions/comparators	Deferasirox (Exjade, ICL670) vs placebo
	Deferasirox vs deferoxamine (Desferal®, DFO, desferioxamine)
	Deferasirox vs deferiprone (Ferripox®)
	Combination therapy (DFO + deferiprone) vs DFO or deferiprone
Outcomes	Absolute and relative change in serum ferritin
	Absolute and relative change in liver iron concentration (LIC)
	Success rate (trial specific based on LIC reduction)
	Cardiac iron (cardiac T2*)
	Quality of life
	Adverse effects of treatment (gastrointestinal disorders, cardiac disorders, etc.)
	Quality-adjusted life-year gained (QALY)
Exclusion criteria	Patients with chronic anaemia not requiring regular transfusion
	Non-English language papers
	Narrative reviews, editorials, opinions

Drummond and Jefferson.[69] Any discrepancies in quality grading were resolved through discussion.

Data synthesis

Data are presented in structured tables and described within the economics review section of this report.

Identification of evidence: longer-term adverse event data

Search strategy

A separate search was undertaken to identify non-RCT adverse event information; details of the search strategy can be found in Appendix 6. This search was not intended to be comprehensive but to provide an overview of the adverse event information available from longer-term non-RCT sources.

Selection of evidence

A non-systematic approach was undertaken to identify the relevant articles, with one reviewer (NF) assessing the identified reports for inclusion. A summary table of relevant studies can be found in Appendix 6.

Data abstraction

Adverse event data from the included studies were abstracted into structured tables by one reviewer (NF) and then checked for accuracy by a second reviewer (JG).

Quality assessment

No quality assessment was undertaken.

Data synthesis

Data are tabulated and narratively discussed within the clinical section of this report.

Chapter 4
Clinical effectiveness

Selection of included trials

A total of 884 non-duplicate records was identified by our search strategy (see Chapter 3 and Appendix 5) and subsequently screened for inclusion in the review. Of these, 213 were identified to which the inclusion criteria were applied. These included 14 trials (reported in 31 publications) making comparisons between deferasirox, DFO, deferiprone and combination therapy (deferiprone and DFO) (see *Table 5*). Data for all of these trials were published in peer-reviewed journals (although two were only presented as abstracts[70,71]) with additional information derived from contacting authors. In the case of deferasirox versus DFO, additional data were retrieved from the US FDA clinical review.[72]

Quality assessment of included trials

The methodological quality of the included trials is presented in *Table 6* using the criteria based on the Centre for Reviews and Dissemination Report No. 4,[66] which include key aspects of RCT design and quality. It should be noted that Ha *et al*.[93] reported on two trials (of well-chelated and poorly-chelated patients) in one paper and so for the purposes of quality assessment there were only 13 trials (although the information was still derived from 31 publications).

Overall, the methodological quality of the included trials was poor. The published papers all stated that patients were randomly allocated to treatment groups; however, only four[77,81,91,93] described the method of randomisation used and only two of these[81,91] noted whether or how allocation was concealed. One other[83] gave details of allocation concealment but did not adequately document the randomisation process. Blinding of administrators or participants was acknowledged to be difficult or unethical given the administration route of the main comparator DFO, but the blinding of assessors was generally addressed inadequately, with only two trials[91,94] providing information in this respect. Intention to treat (ITT) analyses were carried out in four trials;[81,83,91,96] one trial[62] was a non-inferiority trial in which ITT analysis may increase the risk of falsely concluding non-inferiority and thus per protocol analysis (as presented) may be preferable.[100] Baseline characteristics including age and gender, along with outcome variables such as serum ferritin, LIC and other potentially significant factors (number of transfusions or patients who had splenectomies), were provided in eight trials.[46,62,77,81,91,94,96,97] Comparability between groups was achieved in six trials[46,62,81,91,93,97] and partially achieved in four.[71,77,94,96] All trials specified the number of patients originally randomised and provided full or partial details of eligibility criteria. All trials reported outcomes for 80% or more of the patients originally randomised; one[95] failed to adequately account for withdrawals.

Trial characteristics

The included trials involved a total study population of 1480, ranging in size from 13[93] to 586.[62] Two trials[81,91] reported on study populations of up to 200 patients but the majority were populated by less than 100 patients. All but three[83,95,96] were designed as multicentred trials.

Most trials were designed as parallel and open-label studies. Of these, two were three-arm trials.[70,95] There was one double-blind, placebo-controlled, parallel trial[46] and one randomised crossover design.[83]

The duration of each trial varied between 5 days[83] and 2 years[71] with the majority[46,62,77,81,91,94,96,97,101] continuing for approximately 12 months. Three trials were halted prematurely, the two Ha *et al*. RCTs[93] because of the unexpected death of a patient in one of these trials and the third trial[71] because of withdrawal of support from the pharmaceutical company funding the trial.

Outcome measures varied across trials and were surrogate measures of iron overload: serum ferritin; LIC determined by biopsy, SQUID or liver T2*; heart iron content assessed by myocardial T2*.

TABLE 5 *Summary of included trials*

	Study
Deferasirox vs DFO	Cappellini 2006[62,73–76]
	Piga 2006[77–80]
	Vichinsky 2007[81,82]
Deferiprone vs DFO	Olivieri 1992[83–85]
	Olivieri 1997[71,86–90]
	Maggio 2002[91,92]
	Ha 2006(well-chelated patients)[93]
	Pennell 2006[94]
	Gomber 2004[95a]
	Aydinok 2006[70a]
Combination therapy (deferiprone and DFO) vs DFO or deferiprone	Mourad 2003[96]
	Gomber 2004[95]
	Aydinok 2006[70]
	Galanello 2006[97]
	Ha 2006 (poorly chelated patients)[93]
	Tanner 2007[46,98,99]

a These two trials also compared combination therapy versus DFO and deferiprone.

Serum ferritin was the most commonly utilised measure, set as the primary outcome in six trials[91,93,95–97] and the secondary outcome in seven others.[46,62,70,71,77,81,94]

One trial used LIC determined by biopsy to measure the primary outcome;[70] another trial[62] employed LIC determined by biopsy and SQUID as the primary outcome. Of the two trials in which LIC by biopsy was a secondary outcome, one trial set out to measure all patients[93] and one a subset of patients.[91] Two trials employed LIC by SQUID to measure the primary outcome[71,97] and three others used it as a secondary outcome.[77,81,94]

Success in terms of change in LIC was an outcome in two trials.[62,77] In Cappellini *et al*.[62] success was defined in patients with a baseline LIC of < 10 mg Fe/g dw as an end-of-study LIC value of 1–7 mg Fe/g dw and in patients with a baseline LIC of ≥ 10 mg Fe/g dw as a decrease in LIC of ≥ 3 mg Fe/g dw. In Piga *et al*.[77] success was defined as a fall in baseline LIC of $> 10\%$.

Myocardial T2* was the primary outcome in two trials.[46,94] Other outcomes included liver T2*,[46] a range of safety measures,[60,77,81,94,96,97] urinary or faecal iron excretion[83,91,95,96,101] and adherence.[46,70,91,93,94,96,97]

Trials differed in respect of the lower age limits of participants. One trial did not specifically state ages but described patients as 'children'.[95]

At least half (7/14) of the trials received pharmaceutical support.[46,62,71,77,81,94,97]

Trial characteristics are presented in *Table 7*.

Participant characteristics

The majority of trials included patients with beta-TM or thalassaemia (*Table 8*). Two patients with beta-TI were included in one trial[77] and there were two patients with DBA in another.[83] One trial included only patients with SCD.[81] The youngest patient was aged 2 years[62] and the oldest was aged 54 years.[81] Trials were evenly balanced in terms of male and female participants but there were differences across trials in terms of baseline LIC and serum ferritin.

TABLE 6 *Quality assessment*

	Randomisation			Baseline comparability				Blinding				Withdrawals		
Study name	**Truly random**	**Allocation concealment**	**Number stated**	**Presented**	**Achieved**	**Eligibility criteria specified**	**Co-interventions identified**	**Assessors**	**Administration**	**Participants**	**Procedure assessed**	**> 80% in final analysis**	**Reasons stated**	**Intention to treat**
Deferasirox vs DFO														
Cappellini 2006[62,73–76]	N/S	N/S	✓	✓	✓	✓	N/S	×	×	×	N/A	✓	✓	×
Piga 2006[77–80]	✓	N/S	✓	✓	✓/×	✓	N/S	×	×	×	N/A	✓	✓	×
Vichinsky 2007[81,82]	✓	✓	✓	✓	✓	✓	N/S	×	×	×	×	✓	✓	✓[a]
Deferiprone vs DFO														
Olivieri 1992[83–85]	N/S	✓	✓	N/A[b]	N/A	✓/×	✓	N/S	N/S	N/S	N/S	✓	N/A	✓
Olivieri 1997[71,86–90c]	N/S	N/S	✓	✓/×[d]	✓/×	✓/×	N/S	N/S	N/S	N/S	N/S	N/S	✓	N/S
Maggio 2002[91,92]	✓	✓	✓	✓	✓	✓	N/S	✓	×	×	N/S	✓	✓	✓
Pennell 2006[94]	N/S	N/S	✓	✓	✓/×[e]	✓	✓	✓	×	×	N/S	✓	✓	×[f]
Ha 2006[93c]	Because information pertaining to quality assessment was reported for both trials of well-chelated and poorly-chelated patients, all data are presented below under combination therapy vs DFO or deferiprone													
Combination therapy (deferiprone and DFO) vs DFO or deferiprone														
Mourad 2003[96]	N/S	N/S	✓	✓	✓/×	✓/×	N/S	N/S	N/S	N/S	N/S	✓	N/A	✓
Gomber 2004[95]	N/S	N/S	✓	N/S[g]	N/S	✓	N/S	N/S	N/S	N/S	N/S	✓	N/S	×
Aydinok 2006[70h]	N/S	N/S	✓	N/S	N/S	N/S	N/S	N/S	N/S	N/S	N/S	✓	✓	N/S
Galanello 2006[97]	N/S	N/S	✓	✓	✓	✓	N/S	N/S	N/S	N/S	N/S	✓	✓	×
Ha 2006 (well-chelated and poorly-chelated patients)[93c]	✓	N/S	✓	N/S	✓[d]	✓	N/S	×	×	×	N/A	✓	✓	×[c]
Tanner 2007[46,98,99]	N/S	N/S	✓	✓	✓	✓	N/S	N/S	✓	✓	N/S	✓	✓	N/S[i]

✓, yes (item adequately addressed); ×, no (item not adequately addressed); ✓/×, partially (item partially addressed); N/A, not applicable; N/S, not stated.

a All patients included in primary outcome of safety.
b Crossover trial comparability is within each participant.
c Trial halted prematurely.
d Authors claim comparability.
e Differences between groups on serum ferritin measures.
f ITT stated but one patient excluded from final analysis because of missing data.
g Serum ferritin measures reported with significant differences.
h Also includes data from PowerPoint presentation.102
i Patient numbers not given in final results.

TABLE 7 *Trial characteristics*

Study name	*n*, intervention and dose	Study design	Outcomes	Location
Deferasirox vs DFO				
Cappellini 2006[62]	*n* = 586 Deferasirox 5–30 mg/kg/day, *n* = 296: 5 mg/kg/day, *n* = 15; 10 mg/kg/day, *n* = 78; 20 mg/kg/day, *n* = 84; 30 mg/kg/day, *n* = 119 DFO ≥ 20 mg/kg/day, *n* = 290: 20–30 mg/kg/day, *n* = 14; 25–35 mg/kg/day, *n* = 79; 35–50 mg/kg/day, *n* = 91; ≥ 50 mg/kg/day, *n* = 106	Parallel, open-label, non-inferiority trial	Primary: success/failure in maintaining/reducing LIC (biopsy or SQUID) Secondary: change in serum ferritin; net body iron balance; safety and tolerability	Argentina; Belgium; Brazil; Canada; France; Germany; Greece; Italy; Tunisia; Turkey; UK; US
Piga 2006[77]	*n* = 71 Deferasirox 10 mg/kg/day, *n* = 24 Deferasirox 20 mg/kg/day, *n* = 24 DFO 40mg/kg/day, *n* = 23	Parallel, dose-ranging, open-label trial	Primary: safety and tolerability Secondary: effects of deferasirox on LIC (SQUID), serum ferritin, serum iron, transferrin and transferrin saturation	Italy
Vichinsky 2007[81]	*n* = 203 but data only reported on *n* = 195 Deferasirox 5–30 mg/kg/day, *n* = 132 DFO ≥ 20 mg/kg/day, *n* = 63	Parallel, open-label trial	Primary: safety and tolerability Secondary: change in LIC (SQUID) from baseline; change in serum ferritin	Canada; France; Italy; UK; US
Deferiprone vs DFO				
Olivieri 1992[83]	*n* = 20 Deferiprone 50 mg/kg/day, *n* = 20 DFO 50 mg/kg/day, *n* = 20	Crossover trial	Primary: UIE; faecal iron excretion	Canada
Olivieri 1997[71,86,88,90a]	*n* = 71 but data only reported on *n* = 64 Deferiprone 75 mg/kg/day, *n* = N/R DFO 50 mg/kg/day, *n* = N/R	Parallel trial	Primary: change in LIC (biopsy or SQUID) Secondary: change in serum ferritin; adherence	Canada

Inclusion criteria	Exclusion criteria	Follow-up	Trial support
Beta-TM and chronic iron overload from blood transfusions (LIC ≥ 2 mg Fe/g dw) ≥ 2 years old Receiving ≥ eight blood transfusions per year Enrolment irrespective of previous chelation therapy	ALT > 250 U/l during the year before enrolment; chronic hepatitis B; active hepatitis C; previous positive HIV test; elevated serum creatinine; urinary protein–creatinine ratio > 0.5 mg/mg; nephrotic syndrome; uncontrolled hypertension; prolonged corrected QT interval; systemic infection within 10 days; gastrointestinal conditions preventing absorption of an oral medication; concomitant conditions preventing therapy with deferasirox or DFO; history of ocular toxicity related to iron chelation therapy; poor response to DFO or non-adherence with prescribed therapy	1 year	Trial partly funded by Novartis; two authors with financial interest in Novartis; four authors employed by Novartis
Beta-TM with transfusional haemosiderosis; ≥ 18 years old; received a mean daily dose of DFO of 30 mg/kg 5 days/week for 4 weeks before screening; regularly transfused; ≥ two evaluations of serum ferritin of 2.00–8.00 mg/l or SQUID LIC measurement of 5–15 mg Fe/g dw in previous 12 months; for admission to washout (discontinuation of DFO) LIC should be 5–15 mg Fe/g dw; average post-transfusion haemoglobin levels 10.5–13.5 g/dl in previous 12 months before enrolment, including one measurement during washout	AST or ALT > 250 U/l or a creatinine clearance < 80 ml/minute; hypertension; any A–V block, clinically relevant QT interval prolongation, or requiring treatment with digoxin or any drug that could induce prolongation of A–V; diagnosis of cataract or a previous history of clinically relevant ocular toxicity related to iron chelation	48 weeks	Trial supported by Novartis; five authors employed by Novartis; four authors received research support and lecture fees from Novartis
SCD; > 2 years old; iron overload from repeated blood transfusions or sporadically transfused and received ≥ 20 units of packed red blood cells or equivalent; previous chelation not mandatory; serum ferritin ≥ 1.00 mg/l	Elevated serum creatinine > ULN; significant proteinuria; active hepatitis B or C; second and third A–V heart block; QT interval prolongation; therapy with digoxin or similar medications; chelation therapy-associated ocular toxicity	1 year	Four investigators from Novartis; design and execution co-ordinated by Novartis; contributions to analysis and data interpretation by Novartis; assistance in publication of manuscript by Novartis
Transfusion-dependent anaemia with iron overload	N/R	5 days	Independent
N/R	N/R	2 years[b]	Trial sponsored by Apotex

continued

TABLE 7 *Trial characteristics (continued)*

Study name	*n*, intervention and dose	Study design	Outcomes	Location
Maggio 2002[91]	*n* = 144 Deferiprone 75 mg/kg/day, *n* = 71 DFO 50 mg/kg/day 5 days, *n* = 73	Parallel, single blind trial	Primary: reduction of serum ferritin from baseline Secondary: variation of LIC in patients willing to undergo liver biopsy; variation of liver and heart iron content estimated by NMR; heart function as assessed by heart ultrasonography: LVEF, LVSF, ratio of the right ventricle telediastolic to the telesystolic area (mm^3); variation in 24-hour UIE; adherence	Italy
Ha 2006 (well-chelated patients)[93a]	*n* = 13, well chelated Deferiprone 75 mg/kg/day, *n* = 6 DFO 30–60 mg/kg/day, *n* = 7	Parallel, open label trial	Primary: change in serum ferritin Secondary: change in LIC (biopsy); adherence	Hong Kong
Pennell 2006[94]	*n* = 61 Deferiprone 75–100 mg/kg/day, *n* = 29 DFO 50 mg/kg/day, *n* = 32	Parallel, open label trial	Primary: change in myocardial T2* Secondary: cardiac volumes and function; change in LIC (SQUID); change in serum ferritin; safety	Greece; Italy
Combination therapy vs DFO or deferiprone				
Mourad 2003[96]	*n* = 25 Deferiprone 75 mg/kg/day + DFO 2 g/day, *n* = 11 DFO 40–50 mg/kg/day 5–7 days, *n* = 14	Parallel, open label trial	Change in serum ferritin; UIE; safety; adherence	Lebanon
Gomber 2004[95]	*n* = 30 Deferiprone 75 mg/kg/day, *n* = 10 Deferiprone 75 mg/kg/day + DFO 40 mg/kg/day, *n* = 10 DFO 40 mg/kg/day, *n* = 10	Parallel, open label, three-arm trial	Change in serum ferritin; UIE; adherence	India
Aydinok 2006[70c]	*n* = 95 Deferiprone 75 mg/kg/day, *n* = 33 Deferiprone 75 mg/kg/day + DFO 40–50 mg/kg/day, *n* = 32 DFO 40–50 mg/kg/day, *n* = 30	Parallel, three-arm trial	Primary: change in LIC Secondary: change in serum ferritin; UIE; total body iron excretion/iron balance; change in cardiac function; safety including liver toxicity; adherence	Egypt; Turkey

Inclusion criteria	Exclusion criteria	Follow-up	Trial support
Beta-TM patients with serum ferritin 1.50–3.00 mg/l	Known intolerance to one of the trial treatments and rheumatoid factor; serum antinuclear autoantibody; platelet count < 100,000/mm^3 or leukocyte count < 3000/mm^3; severe liver damage indicated by ascites; clinical evidence of heart failure; sepsis; α-interferon treatment	1 year	Independent
Beta-TM on regular blood transfusion and chelation therapies; well chelated defined as LIC ≤ 7 mg Fe/g dw	Refusing to undergo liver biopsy; < 8 years of age; hepatitis C carrier on interferon treatment; active heart failure or an arrhythmia; non-thalassaemic patients; HIV carrier; severe liver failure; unwilling to receive DFO subcutaneously	18 months (median)	Independent
Homozygous beta-TM; > 18 years; regularly transfused; chelated with subcutaneous DFO; no symptoms of heart failure; abnormal (< 20 ms) but not severe (< 8 ms) myocardial T2*; LVEF > 56%	Symptomatic heart failure; myocardial T2* outside required range; LVEF < 56%; liver enzymes > 3× ULN; unsuitable psychological condition; > 36 years; claustrophobia; pretransfusion haemoglobin level < 90 g/l; refused or unable to participate	1 year	Trial supported by Apotex; five authors with financial interest in Apotex; three authors with financial interest in Novartis
Transfusion-dependent beta-TM; haemoglobin > 9 g/dl; non-compliant or unable to afford DFO; receiving DFO subcutaneously < 4 days/week; serum ferritin > 3.00 mg/l	N/R	1 year	N/R
Children with thalassaemia having received > 20 blood transfusions, serum ferritin > 1.50 mg/l	N/R	6 months	N/R
Iron-overloaded patients; ≥ 4 years	Children < 4 years; non-compliant to DFO or deferiprone; known DFO or deferiprone toxicity/intolerance; neutropenia; thrombocytopenia; renal, hepatic or decompensated heart failure; active viral illness treated with interferon-alpha/ribavirin; repeated *Yersinia* infection; HIV positive; pregnancy and nursing; not taking adequate contraceptive precautions if of childbearing age	1 year	N/R

continued

TABLE 7 *Trial characteristics (continued)*

Study name	*n*, intervention and dose	Study design	Outcomes	Location
Galanello 2006[97]	*n* = 60 Deferiprone 75 mg/kg/day + DFO 'prestudy dose', *n* = 30 DFO 'prestudy dose', *n* = 30	Parallel, open label trial	Change in serum ferritin; change in LIC; adherence; safety	Greece; Italy
Ha 2006 (poorly chelated patients)[93a]	*n* = 36 Deferiprone 75 mg/kg/day + DFO 30–60 mg/kg/day, *n* = 20 DFO 30–60 mg/kg/day, *n* = 16	Parallel, open label trial	Primary: change serum ferritin Secondary: variation of LIC (biopsy); adherence	Hong Kong
Tanner 2007[46]	*n* = 65 Deferiprone 75 mg/kg/day + DFO 40–50 mg/kg/day, *n* = 32 DFO 40–50 mg/kg/day + placebo, *n* = 33	Double-blind, parallel, placebo controlled trial	Primary: change in myocardial T2* Secondary: change in liver T2*; change in serum ferritin; change in LV volumes and function; change in brachial artery reactivity (endothelium dependent and independent); change in BNP (Biosite Diagnostics, San Diego, CA) as a marker of heart failure; adherence; adverse events	Italy

ALT, alanine aminotransferase; AST, aspartate aminotransferase ; BNP, B-type natriuretic peptide; CMR, cardiovascular magnetic resonance; LV, left ventricular; LVEF, left ventricular ejection fraction; LVSR, left ventricular shortening fraction; MR, magnetic resonance; N/R, not reported; UIE, urinary iron excretion; ULN, upper limits of normal.
a Trial halted prematurely.
b Mean 22 months for serum ferritin (minimum 18 months).
c Includes information from personal communication including from PowerPoint presentation.[102]

Data analysis

Results have been grouped by treatment(s) and comparators as follows: deferasirox versus DFO; deferiprone versus DFO; combination therapy (deferiprone and DFO) versus DFO and/or versus deferiprone. The following sections provide an overview of the data available from the trials, the comparability across trials and, when possible and appropriate, the results of any meta-analysis conducted. When meta-analyses were not carried out a narrative summary of the study results is provided. Study outcome data are presented in *Table 9*.

Deferasirox versus DFO

Three trials compared deferasirox with DFO.[62,77,81]

Population

There were notable differences between the patient populations and the inclusion/exclusion criteria for the trials. Cappellini *et al*.[62] and Piga *et al*.[77] included patients with thalassaemia (all but two patients diagnosed with beta-TM), whereas Vichinsky *et al*.[81] assessed patients with SCD. Piga *et al*.[77] included patients aged 18 years or over, whereas both Cappellini *et al*.[62] and Vichinsky *et al*.[81] included patients aged 2 years and over. Comparison of patient data in relation to LIC levels is problematic as levels were measured and reported using a mixture of methods (biopsy and SQUID). Mean baseline serum ferritin concentrations were similar across the trials. By far the largest study was that of Cappellini *et al*.,[62] which included more than twice as many subjects than the other two RCTs combined.

Interventions/comparators

In the study of Piga *et al*.[77] patients were assigned to one of two fixed target doses of deferasirox (10 mg/kg/day or 20 mg/kg/day) or to DFO 40 mg/kg/day, regardless of their baseline LIC. However, no patients in this study received the target DFO dose

Inclusion criteria	Exclusion criteria	Follow-up	Trial support
Beta-TM; > 10 years old; serum ferritin 1.00–400 mg/l over previous year; undergoing chelation with subcutaneous DFO	N/R	1 year	Trial sponsored by Apotex
Beta-TM on regular blood transfusion and chelation therapies; poorly chelated defined as LIC > 7 mg Fe/g dw	Refusing to undergo liver biopsy; < 8 years of age; hepatitis C carrier on interferon treatment; active heart failure or an arrhythmia; non-thalassemic patients; HIV carrier; severe liver failure; unwilling to receive DFO subcutaneously	18 months (median)	Independent
Diagnosis of beta-TM; > 18 years; currently maintained on DFO; maintenance of pretransfusion haemoglobin > 9 g/dl; myocardial T2* between 8 and 20 ms; confirmation of effective contraception throughout trial	Received deferiprone for > 6 months in previous 5 years; previous reaction to deferiprone; neutropenia (absolute neutrophil count < 1.5×10^9/l); thrombocytopenia (< 50×10^9/l); liver enzymes > 3x ULN; implant incompatible with MR; claustrophobia; other condition making CMR impossible or inadvisable	1 year	Trial funded by Apotex; five authors received research support from, speaker's honoraria from or acted as a consultant to Apotex/ Novartis

of 40 mg/kg/day although the reasons why were not stated.

In both Cappellini *et al*.[62] and Vichinsky *et al*.[81] deferasirox doses were dependent on baseline LIC and varied between 5 and 30 mg/kg/day.[62,81] DFO target doses were also intended to be based on baseline LIC in Cappellini *et al*.,[62] although the study paper stated that there were four different target doses between 20 and ≥ 50 mg/kg/day. It was noticeable that patients with a baseline LIC of 7 mg Fe/g dw or less received higher mean DFO doses than those defined in the study methods. This is because the study methods allowed for patients who had been taking DFO to remain on their previous doses, which were generally higher than those that were intended to be prescribed for these patients. Thus, DFO doses actually administered ranged from 20 mg/kg/day to 75.6 mg/kg/day in Cappellini *et al*.[62] and from 26.6 mg/kg/day to 31.6 mg/kg/day in Piga *et al*..[77]

To determine drug doses Cappellini *et al*.[62] measured baseline LIC predominantly using invasive liver biopsy techniques, with some limited use of SQUID, mainly in children. In contrast, Vichinsky *et al*.[81] measured LIC by SQUID only. SQUID is not a readily available method for measuring LIC in clinical practice and its validity has also been questioned by the FDA.[72] It was reported in Cappellini *et al*.[62] that, at the three centres used for assessing SQUID, values reported at the Turin site were approximately 20% lower than those obtained at either the Hamburg or Oakland site and, overall, LIC measured by SQUID underestimated LIC measured by biopsy by around 50%.

Thus, given both the opportunity for DFO patients to receive doses higher than stipulated in the trial methods and the opportunity for SQUID to underestimate true LIC, patients in the deferasirox groups with a baseline LIC of 7 mg Fe/g dw or less may have received a suboptimal dose of

TABLE 8 *Participant characteristics*

Study name	Type of anaemia	Gender male	Mean age (SD), years
Deferasirox vs DFO			
Cappellini 2006[62]	Beta-TM	Deferasirox (*n* = 296), 47.3%	Deferasirox (*n* = 296): 17 (9.47), median (range) 15 (2–49)
		DFO (*n* = 290), 49%	DFO (*n* = 290): 17.3 (9.96), median (range) 15.5 (2–53)
Piga 2006[77]	Beta-TM; beta-TI	Deferasirox 10 mg/kg/day (*n* = 24): 33.3%	Deferasirox 10 mg/kg/day (*n* = 24): 23.7 (range 17–33)
		Deferasirox 20 mg/kg/day (*n* = 24): 41.7%	Deferasirox 20 mg/kg/day (*n* = 24): 25.6 (range 19–50)
		DFO (*n* = 23): 43.5%	DFO (*n* = 23): 22. 7 (range 18–29)
Vichinsky 2007[81]	SCD	Deferasirox (*n* = 132): 39.4%	Deferasirox (*n* = 132): median (range) 15 (3–54)
		DFO (*n* = 63): 44.4%	DFO (*n* = 63): median (range) 16 (3–51)
Deferiprone vs DFO			
Olivieri 1992[83]	Beta-TM	N/R	N/R
Olivieri 1997[71,86,88,90]	Thalassaemia	N/R	N/R
Maggio 2002[91]	Beta-TM	Deferiprone (*n* = 71): 52.1%	Deferiprone (*n* = 71): 20 (5.3)
		DFO (*n* = 73): 46.6%	DFO (*n* = 73): 21 (4.2)
Ha 2006[93] (well-chelated patients)	Because baseline data presented for patients who were both well chelated and poorly chelated, all data are presented below under combination therapy vs DFO or deferiprone		
Pennell 2006[94]	Beta-TM	Deferiprone (*n* = 29): 52%	Deferiprone (*n* = 29): 25.1 (3.8)
		DFO (*n* = 32): 50%	DFO (*n* = 32): 26.2 (4.7)

Mean LIC (SD), mg Fe/g dw	Mean serum ferritin (SD), mg/l	GM cardiac T2* (CV), ms	Co-morbidity
Deferasirox: all patients, biopsy or SQUID ($n = 296$): 14.1 (10.0), median (range) 11.3 (2.1–48.1); baseline ≤ 3 mg Fe/g ($n = 15$): 6.2 (1.6), median (range) 5.0 (4.3–8.7); baseline > 3–7 mg Fe/g dw ($n = 78$): 10.2 (1.2), median (range) 10.0 (5.6–16.3); baseline > 7–14 mg Fe/g dw ($n = 84$): 19.4 (1.7), median (range) 20.0 (9.9–21.4); baseline > 14 mg Fe/g dw ($n = 119$): 28.2 (3.5), median (range) 30.0 (11.0–30.0)	Deferasirox: all patients ($n = 296$): 2.77 (1.90), median (range) 2.21 (0.32–12.65)	N/M	N/R
DFO: all patients, biopsy or SQUID ($n = 290$): 13.2 (9.4), median (range) 11.0 (2.1–55.1); baseline ≤ 3 mg Fe/g dw ($n = 14$): 33.9 (9.9), median (range) 30.0 (23.0–52.6); baseline > 3–7 mg Fe/g dw ($n = 79$): 36.7, median (range) 35.0 (22.0–75.6); baseline > 7–14 mg Fe/g dw ($n = 91$): 42.2 (6.6), median (range) 40.8 (21.0–70.0); baseline > 14 mg Fe/g dw ($n = 106$): 51.6 (5.8), median (range) 51.0 (30.0–66.1)	DFO: all patients ($n = 290$): 2.60 (1.84), median (range) 2.09 (0.45–15.28)		
Data presented in graph only	Data presented in graph only	N/M	Splenectomy; hypogonadism; hypothyroidism; hepatitis B; hepatitis C; cardiac disorder
Deferasirox: baseline ≤ 3 mg Fe/g dw ($n = 4$): 2.5 (0.4) SQUID; baseline > 3–7 mg Fe/g dw ($n = 64$): 7.9 (5.5) SQUID; baseline > 7–14 mg Fe/g dw ($n = 46$): 9.8 (1.9) SQUID; baseline > 14 mg Fe/g dw ($n = 18$): 17.5 (3.0) SQUID	Deferasirox ($n = 132$): median (min–max) 3.46 (1.08–12.90)	N/M	Hepatitis B; hepatitis C
DFO: baseline ≤ 3mg Fe/g dw ($n = 6$): 3.9 (3.5) SQUID; baseline > 3–7 mg Fe/g dw ($n = 21$): 5.2 (2.1) SQUID; baseline > 7–14 mg Fe/g dw ($n = 20$): 8.6 (3.0) SQUID; baseline > 14 mg Fe/g dw ($n = 16$): 14.3 (5.4) SQUID	DFO ($n = 63$): median (min–max) 2.83 (1.02–15.58)		
N/R	N/R	N/M	N/R
Deferiprone ($n = 19$): 8.9 (1.2) biopsy or SQUID	Deferiprone (n = N/R): 1.95 (1.23)	N/M	N/R
DFO ($n = 18$): 6.9 (0.9) biopsy or SQUID	DFO (n = N/R): 2.18 (1.32)		
Deferiprone ($n = 20$): 3.4 (5.5) biopsy	Deferiprone ($n = 71$): 2.16 (0.67)	N/M	Splenectomy; anti-HCV positive; cirrhosis; diabetes; hypogonadism; hypothyroidism; hypoparathyroidism
DFO ($n = 15$): 3.5 (3.0) biopsy	DFO ($n = 73$): 2.07 (0.61)		
Deferiprone ($n = 29$): 6.16 (6.0) SQUID	Deferiprone ($n = 29$): 1.79 (1.03)	Deferiprone ($n = 29$): 13.0 (32)	Hepatitis C; splenectomy
DFO ($n = 32$): 6.32 (5.8) SQUID	DFO ($n = 32$): 2.80 (2.44)	DFO ($n = 32$): 13.3 (30)	

continued

TABLE 8 *Participant characteristics (continued)*

Study name	Type of anaemia	Gender male	Mean age (SD), years
Combination therapy (deferiprone and DFO) vs DFO or deferiprone			
Mourad 2003[96]	Beta-TM	Deferiprone + DFO (*n* = 11): 62.6%	Deferiprone + DFO (*n* = 11): 17 (8),[a] median (range) 14 (12–40)[a]
		DFO (*n* = 14): 42.9%	DFO (*n* = 14): 16 (2),[a] median (range) 16 (12–21)[a]
Gomber 2004[95]	Thalassaemia	N/R	N/R
Aydinok 2006[70b]	Beta-TM	All patients (*n* = 95): 53.7%	Deferiprone (*n* = 33): 12.6 (4.5) (range 5–21)
			Deferiprone + DFO (*n* = 32): 13.1 (4.7) (range 5–26)
			DFO (*n* = 30): 12.6 (5.0) (range 5–23)
Galanello 2006[97]	Beta-TM	Deferiprone + DFO (*n* = 29): 55%	Deferiprone + DFO (*n* = 29): 18.7 (4.8)
		DFO (*n* = 30): 40%	DFO (*n* = 30): 19.8 (6.1)
Ha 2006[93] (well-chelated and poorly chelated patients)	Thalassaemia	All patients: 51%	All patients: median (range) 20 (8–40)
		Well-chelated: N/R	Well-chelated: deferiprone, N/R; DFO, N/R
		Poorly-chelated: N/R	Poorly chelated: deferiprone + DFO, N/R; DFO, N/R
Tanner 2007[46]	Beta-TM	Deferiprone + DFO (*n* = 32): 44%	Deferiprone + DFO (*n* = 32): 28.8 (4.2)
		DFO (*n* = 33): 39%	DFO (*n* = 33): 28.7 (5.3)

GM, geometric mean (CV, coefficient of variation); N/M, not measured; N/R, not reported
a Mean (SD) and median (range) calculated from individual patient data.
b All information provided from personal communication including from PowerPoint presentation.[102]
c Information provided from personal communication.

deferasirox in comparison to patients receiving DFO. During the Vichinsky *et al*.[81] trial, in the light of this information from Cappellini *et al*.,[62] the trial was amended after the first 24 patients had been enrolled so that the minimum deferasirox dose was changed from 5 mg/kg/day to 10 mg/kg/day.

Outcomes

Overall, the mean changes in LIC were similar for patients receiving deferasirox and DFO in Cappellini *et al*.,[62] favouring DFO at lower doses and deferasirox at higher doses. Mean changes in LIC were comparable in Piga *et al*.[77] between the 20 mg/kg/day deferasirox dose and DFO but favoured DFO at the 10 mg/kg/day deferasirox dose. For patients with SCD, Vichinsky *et al*.[81] reported a similar reduction in LIC in both groups.[81,82] Clinical advisors to our review suggested that it would be inappropriate to pool data from thalassaemia and SCD patients.

Mean LIC (SD), mg Fe/g dw	Mean serum ferritin (SD), mg/l	GM cardiac T2* (CV), ms	Co-morbidity
N/M	Deferiprone + DFO (n = 11): 4.15 (1.72)[a]	N/M	N/R
	DFO (n = 14): 5.51 (2.38)[a]		
N/M	Deferiprone (n = 11): 2.67 (0.89)	N/M	N/R
	Deferiprone + DFO (n = 10): 3.35 (1.53)		
	DFO (n = 7): 5.08 (1.72)		
Deferiprone (n = 33): 16.2 (5.4)	Deferiprone (n = 33): 3.84 (1.89)	N/M	N/R
Deferiprone + DFO (n = 32): 16.7 (6.3)	Deferiprone + DFO (n = 32): 3.88 (1.61)		
DFO (n = 30): 18.7 (9.8)	DFO (n = 30): 3.34 (1.34)		
Deferiprone + DFO (n = 29): wet weight 1.6 (0.7) SQUID	Deferiprone + DFO (n = 29): 2.05 (0.69)	N/M	Splenectomy
DFO (n = 30): wet weight 1.6 (0.6) SQUID	DFO (n = 30): 2.26 (0.75)		
All patients: N/R	All patients: N/R	N/M	Hepatitis C; splenectomy
Well-chelated: deferiprone, N/R; DFO, N/R	Well-chelated: deferiprone, N/R; DFO, N/R		
Poorly-chelated: deferiprone + DFO, N/R; DFO, N/R	Poorly chelated: deferiprone + DFO, N/R; DFO, N/R		
Deferiprone + DFO (n = 32): liver T2* (ms) 6.8 (5.9);[c] liver T2* (ms) GM (CV) 4.9 (0.52)	Deferiprone + DFO (n = 32): 2.12 (1.74)[c]	Deferiprone + DFO (n = 32): GM (CV) 11.7 (0.08)	Hepatitis C
DFO (n = 33): liver T2* (ms) 6.1 (5.4);[c] liver T2* (ms) GM (CV) 4.2 (0.62)	DFO (n = 33): 1.79 (1.50)[c]	DFO (n = 33): GM (CV) 12.4 (0.11)	

Similarly, the clinical advisors agreed with the FDA report and advised against combining LIC data measured by different methods (biopsy and SQUID). In both Piga *et al.*[77] and Vichinsky *et al.*,[81] LIC was assessed in each patient using only SQUID, whereas in Cappellini *et al.*,[62] LIC was assessed in each patient using the same method as at baseline, i.e. by biopsy in the majority (84%) of patients but by SQUID (16%) in some. Thus, pooling data derived only from SQUID was considered initially but subsequently rejected because the only site used to assess SQUID in Piga *et al.*[77] was the one site that produced LIC readings approximately 20% lower than values obtained at the other two sites in Cappellini *et al.*[62] In addition, a tenth of the patients in Cappellini *et al.*[62] were aged under 6 years; in young children the aim of chelation is to maintain stable low levels as large reductions in LIC may result in chelator toxicity (from either of the chelators).

Cappellini *et al*.[62] and Piga *et al*.[77] also defined changes in LIC as a success based on trial-specific criteria as described earlier. In Cappellini *et al*.[62] the authors concluded that non-inferiority was achieved only in patients who had a baseline LIC of 7 mg Fe/g dw or higher and who had received the higher doses of deferasirox. Subgroup analysis contained within the FDA clinical report[72] showed that this was the case when success was assessed using either biopsy or SQUID or biopsy alone, but not SQUID alone. In Piga *et al*.[77] the success rate was lower in the 10 mg/kg deferasirox group than in the DFO group (45.8% compared with 76.2% respectively) but a comparable proportion of patients at the higher deferasirox dose (20 mg/kg) met the success criteria compared with the DFO group (72.7% and 76.2% respectively).

In Cappellini *et al*.[62] the reduction in serum ferritin was greater for patients receiving DFO than for those receiving deferasirox although differences between the groups were negligible at a deferasirox dose of 30 mg/kg/day. In Piga *et al*.[77] the mean serum ferritin levels remained relatively constant in the DFO and 20 mg/kg/day deferasirox groups but rose slightly in the 10 mg/kg/day deferasirox group.

Of patients with SCD, those receiving DFO demonstrated marginally greater mean reductions in serum ferritin concentrations than those receiving deferasirox.[81]

None of the trials measured myocardial iron by T2*.

Summary: deferasirox versus DFO

Difficulties exist in comparing findings in patients receiving deferasirox with those in patients receiving DFO because of:

- different types of study populations in terms of age and underlying disease
- deferasirox and DFO doses being dependent on baseline LIC in two trials[62,81] but not in the other[77]
- different methods of measuring baseline and end-of-study LIC
- different ways of reporting changes in serum ferritin across the trials.[77]

Nevertheless, data from two trials[62,77] of thalassaemia patients suggest that 20 mg/kg/day deferasirox performs as well as DFO in terms of reduction in LIC. This finding is also supported by trial-specific measures of 'success' of changes in LIC. Amongst patients with SCD, deferasirox is no more efficacious than DFO in terms of reducing LIC.[81]

With the possible exception of the 30 mg/kg/day deferasirox dose in Cappellini *et al*.,[62] changes in serum ferritin appear to be more favourable for both thalassaemia and SCD patients receiving DFO than for those receiving deferasirox.[62,77,81]

No trials measured changes in myocardial iron by T2*.

Deferiprone versus DFO

Five trials compared deferiprone with DFO,[71,83,91,93,94] one of which was a crossover trial.[83] In addition, two three-arm trials[70,95] compared both deferiprone and DFO with combination therapy (deferiprone and DFO) and therefore are included in this section as well as in the section on combination therapy versus DFO or deferiprone.

Population

All trials included patients with thalassaemia with the majority explicitly stating that patients had beta-TM.[70,71,83,91,94] Olivieri and Brittenham[71] intended to include patients with SCD according to an early report by Basran *et al.*;[87] however, subsequent reports refer to patients with beta-TM,[86,88,89] thalassaemia[90] or make no explicit reference to any disease.[71]

Five trials included both children and adults, whereas Gomber *et al.*[95] recruited only children and Pennell *et al.*[94] included only patients aged 18 years and over.

Comparison of baseline LIC is problematic because of differences in how this was measured. Three trials[70,91,93] measured LIC by biopsy, Olivieri and Brittenham[71] measured it by biopsy or SQUID, and Pennell *et al.*[94] measured it by SQUID; the remaining two trials[83,95] did not measure LIC at all. In the three trials that measured LIC by biopsy it was notable that the baseline LIC was higher in Aydinok *et al.*[70] (at least 16 mg Fe/g dw) than in Maggio *et al.*[91] (around 3.5 mg Fe/g dw or less) or Ha *et al.*[93] (7 mg Fe/g dw or less). In Ha *et al.*[93] the baseline LIC was not actually presented but to be included in this trial it was stated that patients had to be well-chelated, which was defined as having a baseline LIC of 7 mg Fe/g dw or less.

Baseline mean serum ferritin concentrations were measured and reported in all but one study (Ha *et al.*[93]) and were varied. In Aydinok *et al.*[70] baseline

DOI: 10.3310/hta13010

TABLE 9 *Outcomes*

Trial name	Mean change in LIC (SD), mg Fe/g dw at 12 months unless otherwise stated	Mean change in serum ferritin (SD), mg/l at 12 months unless otherwise stated	GM for myocardial T2* (CV; % change; *p*-value), ms at 12 months[a]
Deferasirox vs DFO			
Cappellini 2006[62]	Deferasirox 5–30 mg/kg/day, all patients: –2.4 (8.2) biopsy or SQUID ($n = 268$); –3.0 (8.8) biopsy ($n = 224$); +0.5 (2.9) SQUID ($n = 44$)	Deferasirox 5–30 mg/kg/day, all patients: –0.12 (1.31) ($n = 267$)[b]	Deferasirox 5–30 mg/kg/day: N/M
	Deferasirox 5–10 mg/kg/day, baseline < 7 mg Fe/g dw: +4.0 (3.8) biopsy or SQUID ($n = 83$); +5.6 (3.8) biopsy ($n = 52$); +1.4 (2.1) SQUID ($n = 31$)	Deferasirox 5 mg/kg/day, baseline ≤ 3 mg Fe/g dw: +1.19 (0.70) ($n = 15$)	
		Deferasirox 10mg/kg/day. baseline > 3–7 mg Fe/g dw: +0.83 (0.82) ($n = 73$)	
	Deferasirox 20–30 mg/kg/day, baseline ≥ 7 mg Fe/g dw: –5.3 (8.0) biopsy or SQUID ($n = 185$); –5.6 (8.2) biopsy ($n = 172$); –1.5 (3.7) SQUID ($n = 13$)	Deferasirox 20mg/kg/day, baseline > 7–14 mg Fe/g dw: –0.04 (0.72) ($n = 80$)	
		Deferasirox 30mg/kg/day, baseline > 14 mg Fe/g dw: –0.93 (1.42) ($n = 115$)	
	DFO ≥ 20 mg/kg/day, all patients: –2.9 (5.4) biopsy or SQUID ($n = 273$); –3.2 (5.7) biopsy ($n = 230$); –1.1 (1.9) SQUID ($n = 43$)	DFO ≥ 20 mg/kg/day, all patients: –0.45 (1.08) ($n = 272$)[b]	DFO ≥ 20 mg/kg/day: N/M
		DFO 20–30 mg/kg/day, baseline ≤ 3 mg Fe/g dw: +0.21 (0.46) ($n = 13$)	
	DFO 20–35 mg/kg/day, baseline < 7 mg Fe/g dw: +0.13 (2.2) biopsy or SQUID ($n = 87$); +0.5 (2.5) biopsy ($n = 55$); –0.5 (1.3) SQUID ($n = 32$)	DFO 25–35 mg/kg/day, baseline > 3–7 mg Fe/g dw: +0.03 (0.59) ($n = 77$)	
		DFO 35–50 mg/kg/day, baseline > 7–14 mg Fe/g dw: –0.36 (0.61) ($n = 89$)	
	DFO 35–≥50 mg/kg/day, baseline ≥ 7 mg Fe/g dw: –4.3 (5.8) biopsy or SQUID ($n = 186$); –4.4 (6.0) biopsy ($n = 175$); –2.9 (2.3) SQUID ($n = 11$)	DFO ≥ 50 mg/kg/day, baseline > 14 mg Fe/g dw: –1.00 (1.43) ($n = 101$)	
Piga 2006[77]	Deferasirox 10 mg/kg/day: –0.4 (2.2) SQUID at 12 months ($n = 24$);[c] –0.4 (1.7) SQUID at 6 months ($n = 24$)[c]	Deferasirox 10 mg/kg/day: data only presented in graph but this shows that concentration levels remain relatively stable	Deferasirox 10 mg/kg/day: N/M
	Deferasirox 20 mg/kg/day: –2.1 (2.6) SQUID at 12 months ($n = 22$);[c] –1.5 (2.2) SQUID at 6 months ($n = 22$)[c]	Deferasirox 20 mg/kg/day: data only presented in graph but this shows a steady increase in concentration levels	Deferasirox 20 mg/kg/day: N/M
	DFO 40 mg/kg/day: –2.0 (2.0) SQUID at 12 months ($n = 21$);[c] –1.3 (1.8) SQUID at 6 months ($n = 21$)[c]	DFO 40 mg/kg/day: data only presented in graph but this shows that concentration levels remain relatively stable	DFO 40 mg/kg/day: N/M
Vichinsky 2007[81,82]	Deferasirox 5–30 mg/kg/day: adjusted for transfusion category –3.0 (6.2) SQUID ($n = 113$); unadjusted –1.3 (3.1) SQUID ($n = 113$)	Deferasirox 5–30 mg/kg/day: –0.18 (1.65) ($n = 83$)	Deferasirox 5–30 mg/kg/day: N/M
	DFO ≥ 20 mg/kg/day: adjusted for transfusion category –2.8 (10.4) SQUID ($n = 54$); unadjusted –0.7 (2.6) SQUID ($n = 54$)	DFO ≥ 20mg/kg/day: –0.56 (0.95) ($n = 33$)	DFO ≥ 20 mg/kg/day: N/M

continued

TABLE 9 *Outcomes (continued)*

Trial name	Mean change in LIC (SD), mg Fe/g dw at 12 months unless otherwise stated	Mean change in serum ferritin (SD), mg/l at 12 months unless otherwise stated	GM for myocardial T2* (CV; % change; *p*-value), ms at 12 months[a]
Deferiprone vs DFO			
Olivieri 1992[83]	Deferiprone 50 mg/kg/day: N/M	Deferiprone 50 mg/kg/day: N/R	Deferiprone 50 mg/kg/day: N/M
	DFO 50 mg/kg/day: N/M	DFO 50 mg/kg/day: N/R	DFO 50mg/kg/day: N/M
Olivieri 1997[71,86]	Deferiprone 75 mg/kg/day: +4.8 biopsy or SQUID at mean ≥30 months ($n = 19$)[d]	Deferiprone 75 mg/kg/day: –0.27 at mean 22 months (range 18–23 months) ($n = 19$)[d]	Deferiprone 75 mg/kg/day: N/M
	DFO 50 mg/kg/day: +1.0 biopsy or SQUID at mean ≥30 months ($n = 18$)[d]	DFO 50 mg/kg/day: +0.01 at mean 22 months (range 18–23 months) ($n = 18$)[d]	DFO 50 mg/kg/day: N/M
Maggio 2002[91]	Deferiprone 75 mg/kg/day: –1.02 (3.51) biopsy at mean ≥30 months ($n = 20$)	Deferiprone 75 mg/kg/day: –0.22 (0.78) ($n = 71$)	Deferiprone 75 mg/kg/day: N/M
	DFO 50 mg/kg/day: –0.35 (0.52) biopsy at mean ≥30 months ($n = 15$)	DFO 50 mg/kg/day: –0.23 (0.62) ($n = 73$)	DFO 50 mg/kg/day: N/M
Ha 2006 (well-chelated patients)[93]	Deferiprone 75 mg/kg/day: +5.63 (4.24) biopsy at median 18 months ($n = 4$)	Deferiprone 75 mg/kg/day: +0.40 (1.07) at median 18 months ($n = 7$)	Deferiprone 75 mg/kg/day: N/M
	DFO 30–60 mg/kg/day: +2.90 (1.27) biopsy at median 18 months ($n = 2$)	DFO 30–60 mg/kg/day: –0.07 (1.63) at median 18 months ($n = 6$)	DFO 30–60 mg/kg/day: N/M
Pennell 2006[94]	Deferiprone 75–100 mg/kg/day: –0.93 (2.9) SQUID ($n = 27$)	Deferiprone 75–100 mg/kg/day: –0.18 (0.83) at 12 months ($n = 29$); +0.15 (0.71) at 6 months ($n = 29$)	Deferiprone 75–100 mg/kg/day: 16.5 (38%; +27%; $p < 0.001$) at 12 months ($n = 29$)
	DFO 50 mg/kg/day: –1.54 (2.5) SQUID ($n = 30$)	DFO 50 mg/kg/day: –0.47 (0.74) at 12 months ($n = 32$); –0.31 (0.92) at 6 months ($n = 32$)	DFO 50 mg/kg/day: 15.0 (39%; +13%; $p < 0.001$) at 12 months ($n = 31$)
Combination therapy (deferiprone and DFO) vs DFO or deferiprone			
Mourad 2003[96]	Deferiprone 75 mg/kg/day + DFO 2 g/day: N/M	Deferiprone 75 mg/kg/day + DFO 2 g/day: –1.44 (2.09) at 12 months ($n = 11$);[e] –1.15 (2.26) at 6 months ($n = 11$)[e]	Deferiprone 75 mg/kg/day + DFO 2 g/day: N/M
	DFO 40–50 mg/kg/day: N/M	DFO 40–50 mg/kg/day: –1.51 (1.67) at 12 months ($n =$);[e] –0.65 (1.55) at 6 months ($n =$)[e]	DFO 40–50 mg/kg/day: N/M

DOI: 10.3310/hta13010

Trial name	Mean change in LIC (SD), mg Fe/g dw at 12 months unless otherwise stated	Mean change in serum ferritin (SD), mg/l at 12 months unless otherwise stated	GM for myocardial T2* (CV; % change; *p*-value), ms at 12 months[a]
Gomber 2004[95]	Deferiprone 75 mg/kg/day: N/M	Deferiprone 75 mg/kg/day: +0.75 (1.16) at 6 months (*n* = 11)	Deferiprone 75 mg/kg/day: N/M
	Deferiprone 75 mg/kg/day + DFO 40 mg/kg/day: N/M	Deferiprone 75mg/kg/day + DFO 40 mg/kg/day: +0.03 (0.92) at 6 months (*n* = 10)	Deferiprone 75 mg/kg/day + DFO 40mg/kg/day: N/M
	DFO 40 mg/kg/day: N/M	DFO 40 mg/kg/day: –1.36 (1.37) at 6 months (*n* = 7)	DFO 40 mg/kg/day: N/M
Aydinok 2006[70b]	Deferiprone 75 mg/kg/day: –5.7 (8.6) biopsy (*n* = 29)[b]	Deferiprone 75 mg/kg/day: –1.43 (1.69) (*n* = 30)[b]	Deferiprone 75 mg/kg/day: N/M
	Deferiprone 75 mg/kg/day + DFO 40–50 mg/kg/day: –9.9 (8.9) biopsy (*n* = 24)[b]	Deferiprone 75 mg/kg/day + DFO 40–50 mg/kg/day: –1.72 (1.32) (*n* = 26)[b]	Deferiprone 75 mg/kg/day + DFO 40–50 mg/kg/day: N/M
	DFO 40–50 mg/kg/day: –9.6 (8.7) biopsy (*n* = 19)[b]	DFO 40–50 mg/kg/day: –0.54 (0.95) (*n* = 25)[b]	DFO 40–50 mg/kg/day: N/M
Galanello 2006[97]	Deferiprone 75 mg/kg/day + DFO 'prestudy dose': wet weight –65 (615) SQUID (*n* = 29)	Deferiprone 75 mg/kg/day + DFO 'prestudy dose': –0.25 (0.79) (*n* = 29)	Deferiprone 75 mg/kg/day + DFO 'prestudy dose': N/M
	DFO 'prestudy dose': wet weight –239 (474) SQUID (*n* = 30)	DFO 'prestudy dose': +0.35 (0.57) (*n* = 30)	DFO 'prestudy dose': N/M
Ha 2006(poorly-chelated patients)[93]	Deferiprone 75 mg/kg/day + DFO 30–60 mg/kg/day: +0.95 (15.49) biopsy at median 18 months (*n* = 8)	Deferiprone 75mg/kg/day + DFO 30–60 mg/kg/day: –0.99 (2.98) at median 18 months (*n* = 17)	Deferiprone 75mg/kg/day + DFO 30–60 mg/kg/day: N/M
	DFO 30–60 mg/kg/day: +0.82 (8.25) biopsy at median 18 months (*n* = 5)	DFO 30–60 mg/kg/day: +1.06 (2.29) at median 18 months (*n* = 14)	DFO 30–60 mg/kg/day: N/M
Tanner 2007[46]	Deferiprone 75 mg/kg/day + DFO 40–50 mg/kg/day, liver T2* (ms) GM (CV; ratio of GM; *p*-value) at 12 months: 10.7 (37%; 2.07; $p < 0.001$) (*n* = 28)[b]	Deferiprone 75 mg/kg/day + DFO 40–50 mg/kg/day: –0.95 (*n* = 28)[b,d]	Deferiprone 75 mg/kg/day + DFO 40–50 mg/kg/day: 17.7 (37%; +51%; $p < 0.001$) (*n* = 29)
	DFO 40–50 mg/kg/day + placebo, liver T2* (ms) GM (CV; ratio of GM; *p*-value) at 12 months: 5.0 (13%; 1.50; $p = 0.01$) (*n* = 30)[b]	DFO 40–50 mg/kg/day + placebo: –0.22 (*n* = 30)[b,d]	DFO 40–50 mg/kg/day + placebo: 15.7 (50%; +27%; $p = 0.001$) (*n* = 31)

GM, geometric mean; N/M, not measured; N/R, not reported.
a Unlike mean changes in serum ferritin and LIC in which the larger the negative result, the better, for myocardial T2* the larger the positive result, the better.
b Data provided by author.
c Data derived from FDA clinical review.[72]
d Data derived by taking away end-of-trial measure from baseline measure, hence SD not always calculable.
e Data derived from individual patient data.

levels were higher in both groups (deferiprone, 3.84 mg/l; DFO, 3.34 mg/l) and in Gomber *et al.*[95] they differed between the two groups (deferiprone, 2.67 mg/l; DFO, 5.08 mg/l). In Maggio *et al.*[91] inclusion criteria stated that patients must have a baseline serum ferritin of between 1.50 mg/l and 3.00 mg/l, although 11 patients in the deferiprone group and seven patients in the DFO group had baseline levels of 3.00 mg/l or above.

Interventions/comparators

Deferiprone target doses were the same (75 mg/kg/day) in five of the seven trials but in Pennell *et al.*[94] a higher dose (75 mg/kg/day rising to a target dose of 100 mg/kg/day) was given and in Olivieri *et al.*[83] a lower dose was given (50 mg/kg/day). DFO target doses were relatively similar in all of the trials (40 mg/kg/day,[95] 50 mg/kg/day[71,83,91,94] or a range between 40 and 50 mg/kg/day[70] or 30 and 60 mg/kg/day[93]).

In Olivieri *et al.*[83] patients acted as their own controls. Thus, they were admitted to hospital and given either deferiprone or DFO on days two, three and four. On day six patients were discharged and readmitted 3–4 weeks later following their next blood transfusion and given the alternative drug in the same manner. In all of the other trials deferiprone was taken orally three times a day, 7 days a week and DFO was infused, often overnight, between five and seven times a week.

Outcomes

Five trials measured mean changes in LIC[70,71,91,93,94] but different measures of LIC were used across the trials. Changes were also assessed over different time periods, varying from 12 months[70,94] to a median of 18 months[93] to a mean of around 30 months or more.[71,91] These variations made it impossible to pool these data.

Findings were not consistent across the trials. Olivieri and Brittenham[71] and Ha *et al.*[93] reported increases in LIC for both the deferiprone and DFO groups over a period of 18 months or more, with smaller increments in the DFO group, whereas Maggio *et al.*[91] and Pennell *et al.*[94] reported decreases in LIC that were reasonably similar for both groups. Aydinok *et al.*[70] also reported decreases in both groups but the decrease was larger in the DFO group.

Six trials measured mean changes in serum ferritin[70,86,91,94–96] although again over different time periods varying from 6 months[95] to 12 months,[70,91,94] a median of 18 months[93] and a mean of 22 months.[86] Again, findings were not consistent across the trials. At 12 months or more most trials reported a decrease amongst patients in both groups whereas, at 6 months, both Gomber *et al.*[95] and Pennell *et al.*[94] reported decreases in the DFO group as opposed to increases in the deferiprone group.

Data could be pooled for two trials at 6 months (*Figure 4*)[94,95] and three trials at 12 months (*Figure 5*).[70,91,94] The pooled estimate was not significant but does appear to favour DFO at 6 months [random effects, weighted mean difference (WMD) 1.18, 95% confidence interval (CI) –0.42 to 2.78]; there was no significant difference in serum ferritin between the deferiprone and DFO groups at 12 months (random effects, WMD –0.10, 95% CI –0.57 to 0.38). However, the trials showed statistical heterogeneity at both time points (6 months: $\chi^2 = 6.27$, df = 1, $p = 0.01$, $I^2 = 84.0\%$; 12 months: $\chi^2 = 8.09$, df = 2, $p = 0.02$, $I^2 = 75.3\%$).

Only Pennell *et al.*[94] measured myocardial iron using T2*. This study reported both deferiprone and DFO to be efficacious in removing myocardial iron and the authors also reported that the difference between drugs was significant in favour of deferiprone at both 6 months (ratio of geometric mean, 1.09; $p = 0.040$) and 12 months (ratio of geometric mean, 1.12; $p = 0.023$).

All of the trials were concerned with measuring the control of iron overload except for the Olivieri *et al.* crossover trial.[83] Thus, this trial did not report on any relevant outcomes, although it did measure serum ferritin concentrations. However, given the short-term nature of this trial (5 days), any reported outcomes of this measure would have been of limited clinical value.

Summary: deferiprone versus DFO

Comparing patients receiving deferiprone with those receiving DFO is problematic because:

- although five trials included patient populations consisting of a mixture of children and adults,[70,71,83,91,93] one study focused only on children[95] and another only on adults[94]
- not all trials measured LIC and, in those that did, different methods and time points were used.

Based on mixed populations of children and adults the findings suggest that there was no significant difference between deferiprone and DFO in terms of changes in serum ferritin at 6 months[94,95]or 12

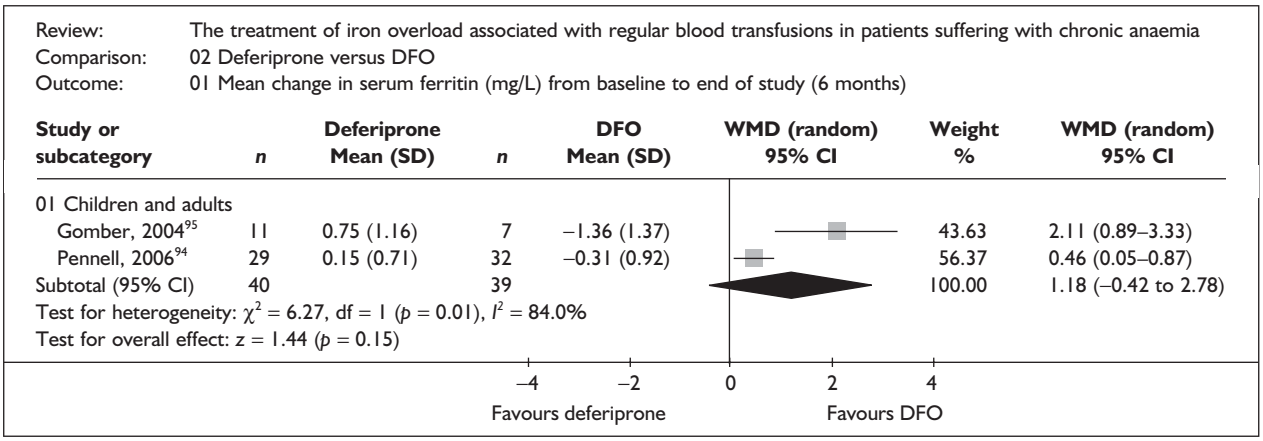

FIGURE 4 *Pooled mean changes in serum ferritin (mg/l) in trials comparing deferiprone with DFO at 6 months.*

months[70,91,94] although statistical heterogeneity was evident.

Myocardial iron was assessed by T2* in one study[94] (of adults) and reported deferiprone to be significantly superior to DFO, suggesting a superior outcome in terms of removing iron from the heart.

Combination therapy (deferiprone and DFO) versus DFO or deferiprone

Six trials evaluated combination therapy versus DFO,[46,70,93,95–97] of which two also considered combination therapy versus deferiprone.[70,95]

Population

All trials included patients with thalassaemia with most explicitly stating that patients had beta-TM.[46,70,96,97] The majority included a mix of children and adults although Gomber *et al.*[95] included only children and Tanner *et al.*[46] included only patients aged 18 years and over. Thus, mean ages at baseline ranged from around 13 years in Aydinok *et al.*[70] to nearly 29 years in Tanner *et al.*[46] Average ages in the other trials (except Gomber *et al.*[95] in which the average age of patients was not stated) were between 16 and 20 years depending on treatment group.

Comparison of baseline LIC remains difficult because of differences in measurement. Two trials measured LIC by biopsy,[70,93] Galanello *et al.*[97] measured LIC by SQUID and Tanner *et al.*[46] used liver T2*. The remaining two trials[95,96] did not measure LIC.

Of the two trials using biopsy, baseline LIC was 16 mg Fe/g dw or higher in Aydinok *et al.*,[70] whereas Ha *et al.*[93] simply reported that patients had to be

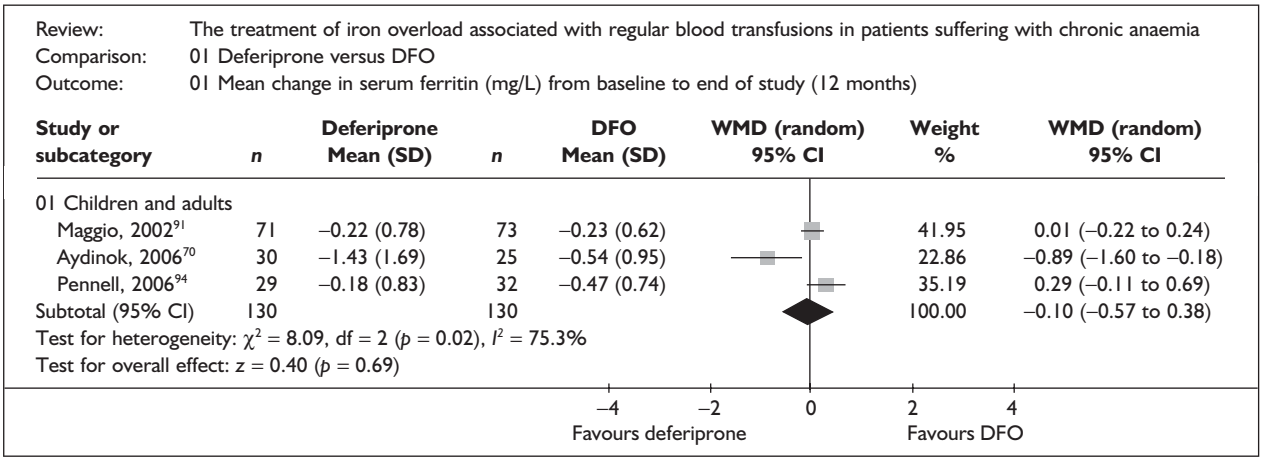

FIGURE 5 *Pooled mean changes in serum ferritin (mg/l) in trials comparing deferiprone with DFO at 12 months.*

poorly chelated, which was defined as having a baseline LIC of greater than 7 mg Fe/g dw.

Baseline serum ferritin varied across the trials, reflecting varied inclusion/exclusion criteria. Thus, the baseline serum ferritin ranged between 2.67 mg/l (deferiprone) and 5.08mg/l (DFO) in Gomber *et al.*[95] and between 4.15mg/l (combination therapy) and 5.51mg/l (DFO) in Mourad *et al.*[96] and was around 2.00 mg/l (in both groups) in Galanello *et al.*[97] Baseline levels were close to 2.00 mg/l (in both groups) in Tanner *et al.*[46] and 3.50 mg/l in Aydinok *et al.*[70] Ha *et al.*[93] did not report baseline levels.

Interventions/comparators

In all trials deferiprone target doses were the same (75 mg/kg/day) for combination therapy[46,70,93,95–97] and, when applicable, for deferiprone monotherapy.[70,95] DFO doses were also comparable across the trials (40–50 mg/kg/day), either as monotherapy or in combination with deferiprone. Tanner *et al.*[46] was the only study in which a placebo pill was given with DFO as a comparator to combination therapy.

Outcomes

All of the trials that measured LIC[46,70,93,97] reported similar changes in LIC between the groups irrespective of how LIC was measured. In Aydinok *et al.*[70] the mean fall in LIC was greater in the combination therapy group than in the deferiprone monotherapy group. Change in LIC data could not be pooled because of the different methods and time points of measurement.

All six trials[46,70,93,95–97] measured mean change in serum ferritin. Over 6 months Gomber *et al.*[95] and Mourad *et al.*[96] reported findings supporting DFO and combination therapy, respectively, but overall the pooled estimate from the two trials suggested no significant difference (random effects, WMD 0.52, 95% CI –1.33 to 2.37; *Figure 6*). Over 12 months three trials reported combination therapy to be marginally superior to DFO in terms of the mean reduction in serum ferritin concentrations,[46,70,97] whereas another trial reported DFO to be superior.[96] Data could only be pooled for three of these trials[70,96,97] (*Figure 7*) because change in standard deviation data were not available and could not easily be calculated for Tanner *et al.*[46] The meta-analysis found a significantly larger decrease in mean serum ferritin in the combination therapy group than in the DFO group (fixed effects, WMD –0.71, 95% CI –1.01 to –0.41).

Two trials compared combination therapy with deferiprone monotherapy.[70,95] Both reported combination therapy to be superior in terms of change in serum ferritin; over 6 months in Gomber *et al.*[95] and 12 months in Aydinok *et al.*[70]

Only one study[46] measured myocardial iron using T2*. Tanner *et al.*[46] reported significant improvements in myocardial T2* over 6 and 12 months in both the combination therapy group and the DFO group with the combination therapy group performing significantly better than the DFO group (increase of 10%, 95% CI 2–19%; $p = 0.02$).

Summary: combination therapy versus DFO or deferiprone

Comparing patients and measuring changes in LIC in those receiving combination therapy with

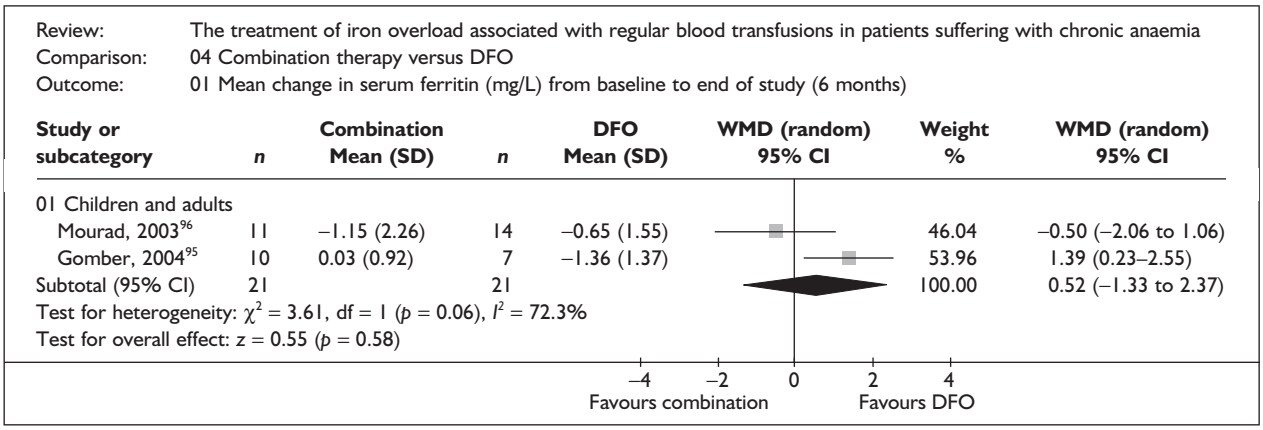

FIGURE 6 *Pooled mean changes in serum ferritin (mg/l) in trials comparing combination therapy with DFO at 6 months.*

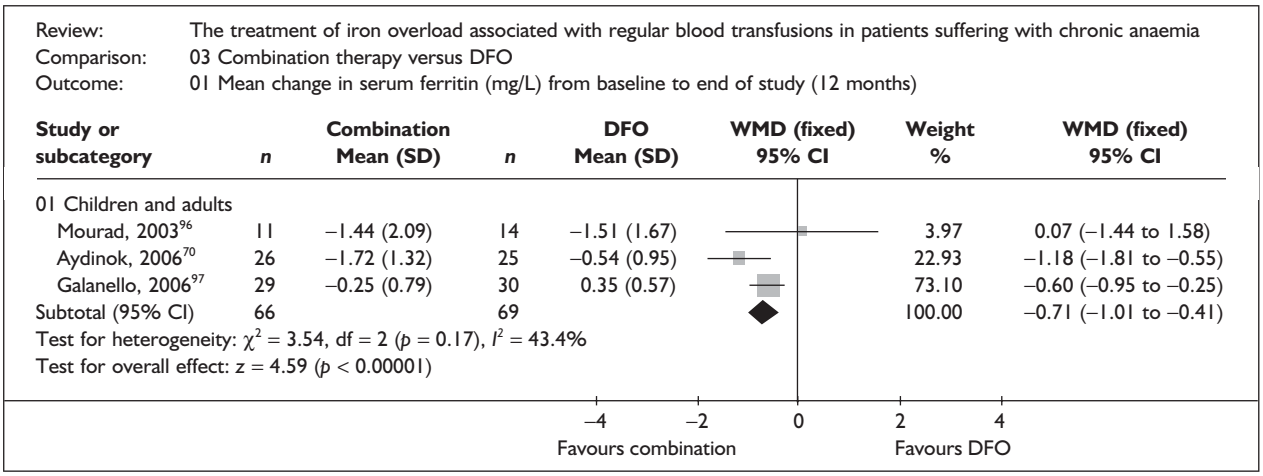

FIGURE 7 *Pooled mean changes in serum ferritin (mg/l) in trials comparing combination therapy with DFO at 12 months.*

those receiving DFO monotherapy or deferiprone monotherapy is problematic because:

- although four trials included patient populations consisting of a mixture of children and adults,[70,93,96,97] one study focused only on children[95] and another only on adults[46]
- only Aydinok *et al.*[70] and Gomber *et al.*[95] made direct comparisons between combination therapy and DFO but in populations of children and adults and children only respectively
- in trials that measured LIC, different methods and time points were reported
- only two trials compared combination therapy with deferiprone and at different follow-up periods.

Data that could be pooled for change in serum ferritin at 6 months[95,96] and 12 months[70,96,97] suggested there were no significant differences between combination therapy and DFO at 6 months but that combination therapy was significantly superior at 12 months.

Myocardial iron by T2* was assessed in one study (of adults) and reported combination therapy to be significantly superior to DFO.[46]

Adverse events from RCTs

Inconsistent reporting of adverse events (AEs) in the included trials made it difficult to compare these events across the trials (*Table 10*).

Deferasirox versus DFO

The majority of thalassaemia patients in both the deferasirox and DFO groups experienced an AE, most commonly GI events, which were more prevalent in the deferasirox groups than in the DFO groups.[62,72,77] Neutropenia was experienced only by one patient receiving deferasirox in any of the trials whereas skin rash was experienced by around one in ten patients receiving deferasirox. Very few AEs resulted in discontinuation from the study drug in any of the trials.

Severe adverse events (SAEs) were relatively uncommon, infections and infestations and GI events being the most common SAEs in both groups. There were four deaths in the Cappellini *et al.*[62] trial (three in the DFO group), none of which were considered to be drug related by the Program Safety Board.

Other notable events experienced across both beta-TM trials included an increase in creatinine levels, usually mild and stable; very rarely was this noted at consecutive visits.

All of the above results seemed to be mirrored in SCD patients,[81] although a notable SAE here was sickle cell anaemia with crisis experienced by around one-third of all patients in either treatment group (44/132 in deferasirox group; 20/63 in DFO group).

Deferiprone versus DFO

Because some trials did not consider groups of patients receiving deferiprone separately from

TABLE 10 *Adverse events reported in the RCTs*

Trial name	Any AEs and some of the most common	Any SAEs and some of the most common	AEs resulting in temporary or permanent discontinuation	Other notable events
Deferasirox versus DFO				
Cappellini 2006[62a]	Deferasirox 5–30 mg/kg/day: any 254/296 (85.8%); GI 126/296 (42.6%); abdominal pain 41/296 (13.9%); nausea 31/296 (10.5%); vomiting 30/296 (10.1%); diarrhea 35/296 (11.8%); skin rash 25/296 (8.4%); respiratory 80/296 (27.0%); cough 41/296 (13.9%); nasopharyngitis 39/296 (13.2%); viral infection 3/296 (1.0%); arthralgia 22/296 (7.4%); back pain 17/296 (5.7%)	Deferasirox 5–30 mg/kg/day: any 27/296 (9.1%);[b] infections and infestations 7/296 (2.4%); GI disorders 4/296 (1.4%); general disorders 5/296 (1.7%); injury, etc. 5/296 (1.7%); cardiac disorders 2/296 (0.7%); neutropenia 1/296 (0.3%); renal and urinary disorders 0/296; skin disorders 2/296 (0.7%); death 1/296 (0.3%); other 14/296 (4.7%)	Deferasirox 5–30 mg/kg/day: 8/296 (2.4%)	Deferasirox 5–30 mg/kg/day: mild creatinine rise 113/296 (38.2%); serious creatinine rise 29/296 (9.8%); creatinine > 33% at ≥ two consecutive post-baseline visits 106/296 (35.8%); creatinine > 33% and > ULN at ≥ two consecutive post-baseline visits 7/296 (2.4%)
	DFO ≥ 20 mg/kg/day: any 246/290 (84.8%); GI 91/290 (31.4%); abdominal pain 28/290 (9.7%); nausea 14/290 (4.8%); vomiting 28/290 (9.7%); diarrhea 21/290 (7.2%); skin rash 9/290 (3.1%); respiratory 102/290 (35.2%); cough 41/290 (13.9%); nasopharyngitis 42/290 (14.5%); viral infection 2/290 (1.9%); arthralgia 14/290 (4.8%); back pain 32/290 (11.0%)	DFO ≥ 20 mg/kg/day: any 25/290 (8.6%);[b] infections and infestations 9/290 (3.1%); GI disorders 5/290 (1.7%); general disorders 2/290 (0.7%); injury, etc. 3/290 (1.0%); cardiac disorders 3/290 (1.0%); neutropenia 0/290; renal and urinary disorders 2/290 (0.7%); skin disorders 0/290; death 3/290 (1.0%); other 14/290 (4.8%)	DFO ≥ 20 mg/kg/day: 4/290 (1.4%)	DFO ≥ 20 mg/kg/day: mild creatinine rise 41/290 (14.1%); serious creatinine rise 0/290; creatinine > 33% at ≥ two consecutive post-baseline visits 40/290 (13.8%); creatinine > 33% and > ULN at ≥ two consecutive post-baseline visits 1/290 (0.3%)
Piga 2006[77a]	Deferasirox 10–20 mg/kg/day: any 47/48 (97.9%), most common experienced by ≥ four patients in any arm; GI 36/48 (75.0%); abdominal pain 17/48 (35.4%);[c] nausea 10/48 (20.8%); vomiting 8/48 (16.7%); diarrhoea 13/48 (27.1%); skin rash 7/48 (14.6%); respiratory 31/48 (64.6%); cough 15/48 (31.3%); nasopharyngitis 17/48 (35.5%); arthralgia 6/48 (12.5%); back pain 18/48 (37.5%)	Deferasirox 10–20 mg/kg/day: any 7/48 (14.6%); GI 1/48 (2.1%); infections and infestations 2/48 (4.2%); general disorders 1/48 (2.1%); renal and urinary disorders 1/48 (2.1%); hepatobiliary disorders 1/48 (2.1%); injury, etc. 1/48 (2.1%); investigations 0/48; vascular disorders 1/48 (2.1%)	Deferasirox 10–20 mg/kg/day: 1/48 (2.1%)	Deferasirox 10–20 mg/kg/day: creatinine rise > ULN 4/48 (8.3%); consecutive measurements > ULN 0/48
	DFO 40 mg/kg/day: any 21/23 (91.3%), most common experienced by ≥ four patients in any arm; GI 13/23 (56.5%); abdominal pain 4/23 (17.4%);[c] nausea 2/23 (8.7%); vomiting 2/23 (8.7%); diarrhoea 6/23 (26.1%); skin rash 1/23 (4.3%); respiratory 11/23 (47.8%); cough 4/23 (17.4%); nasopharyngitis 8/23 (34.8%); arthralgia 3/23 (13.0%); back pain 8/23 (34.8%)	DFO 40 mg/kg/day: any 5/23 (21.7%); infections and infestations 2/23 (8.7%); GI disorders 2/23 (8.7%); infections and infestations 1/23 (4.3%); general disorders 1/23 (4.3%); renal and urinary disorders 0/23; hepatobiliary disorders 0/23; injury, etc. 0/23; investigations 1/23 (4.3%); vascular disorders 0/23	DFO 40 mg/kg/day: 2/23 (8.7%)	DFO 40 mg/kg/day: creatinine rise > ULN 2/23 (8.7%); consecutive measurements > ULN 0/23

DOI: 10.3310/hta13010

Trial name	Any AEs and some of the most common	Any SAEs and some of the most common	AEs resulting in temporary or permanent discontinuation	Other notable events
Vichinsky 2007[81]	Deferasirox 5–30 mg/kg/day: any N/R, most common in > 10% patients in any arm; sickle cell anaemia with crisis 44/132 (33.3%); abdominal pain 37/132 (28.0%); nausea 30/132 (22.7%); vomiting 28/132 (21.2%); diarrhoea 26/132 (19.7%); skin rash 18/132 (13.6%); cough 18/132 (13.6%); nasopharyngitis 18/132 (13.6%); viral infection 6/132 (4.5%); arthralgia 20/132 (15.2%); back pain 24/132 (18.2%)	Deferasirox 5–30 mg/kg/day: any 61/132 (46.2%); sickle cell anaemia with crisis 44/132 (33.3%); other 17/132 (12.9%)	Deferasirox 5–30 mg/kg/day: 7/132 (5.3%)	Deferasirox 5–30 mg/kg/day: mild stable creatinine rise 48/132 (36.4%); creatinine rise > ULN 3/132 (2.3%)
	DFO ≥ 20 mg/kg/day: any N/R, most common in > 10% patients in any arm; sickle cell anaemia with crisis 20/63 (31.7%); abdominal pain 9/63 (14.3%); nausea 7/63 (11.1%); vomiting 10/63 (15.9%); diarrhoea 3/63 (4.8%); skin rash 3/63 (4.8%); cough 13/63 (20.6%); nasopharyngitis 13/63 (20.6%); viral infection 7/63 (11.1%); arthralgia 9/63 (14.3%); back pain 4/63 (5.9%)	DFO ≥ 20 mg/kg/day: any 27/63 (42.9%); sickle cell anaemia with crisis 20/63 (31.7%); other 7/63 (11.1%)	DFO ≥ 20 mg/kg/day: 2/63 (3.2%)	DFO ≥ 20 mg/kg/day: mild stable creatinine rise 14/63 (22.2%); creatinine rise > ULN 2/63 (3.2%)
Deferiprone vs DFO				
Olivieri 1992[83]	Deferiprone 50 mg/kg/day: any N/R; neutropenia 1/20 (5.0%)	Deferiprone 75 mg/kg/day: N/R	Deferiprone 50 mg/kg/day: N/R	Deferiprone 75 mg/kg/day: N/R
	DFO 5 0mg/kg/day: any N/R	DFO 50 mg/kg/day: N/R	DFO 50 mg/kg/day: N/R	DFO 50 mg/kg/day: N/R
Olivieri 1997[71]	Deferiprone 75 mg/kg/day, resulting in trial withdrawal: neutropenia 3/15 (20.0); agranulocytosis 2/15 (13.3%)	Deferiprone 75 mg/kg/day: N/R	Deferiprone 75 mg/kg/day: 5/15 (33.3%)	Deferiprone 75 mg/kg/day: N/R
	DFO 50 mg/kg/day, resulting in trial withdrawal: neutropenia 0/29; agranulocytosis 0/29	DFO 50 mg/kg/day: N/R	DFO 50 mg/kg/day: 3/11 (27.3%)	DFO 50 mg/kg/day: N/R
Maggio 2002[91]	Deferiprone 75 mg/kg/day: any 24/71 (33.8%); hypertransaminasaemia 16/71(22.5%); nausea 3/71 (4.2%); leukocytopenia 2/71 (2.8%); other N/R	Deferiprone 75 mg/kg/day: any N/R	Deferiprone 75 mg/kg/day: 5/73 (6.8%)	Deferiprone 75 mg/kg/day: ALT change, mean (SD) (U/l) 58 (61) to 80 (125)
	DFO 50 mg/kg/day: any 11/73 (15/1%); pain/erythema at injection site 6/73 (8.2%); other N/R	DFO 50 mg/kg/day: N/R	DFO 50 mg/kg/day: 0/73	DFO 50 mg/kg/day: ALT change, mean (SD) (U/l) 50 (47) to 48 (46)

continued

TABLE 10 *Adverse events reported in the RCTs (continued)*

Trial name	Any AEs and some of the most common	Any SAEs and some of the most common	AEs resulting in temporary or permanent discontinuation	Other notable events
Ha 2006 (well-chelated patients)[93]	Because poorly-chelated and well-chelated patients and thus combination therapy and deferiprone monotherapy are combined with regard to discussion of adverse events in the published paper, all data are presented below under Combination therapy vs DFO or deferiprone			
Pennell 2006[94]	Deferiprone 75–100 mg/kg/day: any N/R; GI 19/29 (65.5%); neutropenia 1/29 (3.4%); other N/R	Deferiprone 75–100 mg/kg/day: N/R	Deferiprone 75–100 mg/kg/day: N/R	No significant difference between groups at 12 months and no significant difference in trend of ALT level over time between groups and difference in percentage of patients with ALT > 2× ULN was not significant between groups
	DFO 50 mg/kg/day: any N/R; reactions at the infusion site 12/32 (37.5%); neutropenia 0/32; other N/R	DFO 50 mg/kg/day: N/R	DFO 50 mg/kg/day: N/R	
Combination therapy (deferiprone and DFO) vs DFO or deferiprone				
Mourad 2003[96]	Deferiprone 75 mg/kg/day + DFO 2 g/day: any N/R; nausea 5/11 (45.5%); joint problems 3/11 (27.3%); neutropenia 0/11; other N/R	Deferiprone 75 mg/kg/day + DFO 2 g/day: N/R	Deferiprone 75 mg/kg/day + DFO 2 g/day: 0/11	Deferiprone 75 mg/kg/day + DFO 2 g/day: N/R
	DFO 40–50 mg/kg/day: any N/R; itching, erythema, swelling and induration at the site of infusion 12/14 (85.7%); other N/R	DFO 40–50mg/kg/day: N/R	DFO 40–50mg/kg/day: N/R	DFO 40–50mg/kg/day: N/R
Gomber 2004[95]	Deferiprone 75 mg/kg/day or deferiprone 75 mg/kg/day + DFO 40 mg/kg/day[d]: any 2/21 (9.5%); arthropathy 2/21 (9.5%); agranulocytosis 0; thrombocytopenia 0	Deferiprone 75 mg/kg/day or deferiprone 75 mg/kg/day + DFO 40 mg/kg/day[d]: any N/R	Deferiprone 75 mg/kg/day or deferiprone 75 mg/kg/day + DFO 40 mg/kg/day[d]: 2/21 (9.5%)	Deferiprone 75 mg/kg/day or deferiprone 75 mg/kg/day + DFO 40 mg/kg/day[d]: N/R
	DFO 40 mg/kg/day: 0/7	DFO 40 mg/kg/day: any 0/7	DFO 40 mg/kg/day: 0/7	DFO 40 mg/kg/day: N/R
Aydinok 2006[70e]	Deferiprone 75 mg/kg/day: any N/R; nausea/vomiting 11/30 (36.6%); skin reactions/allergy 0/30; other N/R	Deferiprone 75 mg/kg/day: any N/R; neutropenia 1/32 (3.3%); agranulocytosis 1/32 (3.3%); death 0/32; other N/R	Deferiprone 75 mg/kg/day: 2/30 (6.7%)	Deferiprone 75 mg/kg/day: mean ALT levels fluctuated during the trial but were lower at the end of the trial than at baseline
	Deferiprone 75 mg/kg/day + DFO 40–50 mg/kg/day; any N/R; nausea/vomiting 5/29; skin reactions/allergy 3/29; other N/R	Deferiprone 75 mg/kg/day + DFO 40–50 mg/kg/day: any N/R; neutropenia 1/29 (3.4%); agranulocytosis 1/29 (3.4%); death 1/29 (3.4%); other N/R	Deferiprone 75 mg/kg/day + DFO 40–50 mg/kg/day: 2/29 (6.9%)	Deferiprone 75 mg/kg/day + DFO 40–50 mg/kg/day: mean ALT levels fluctuated during the trial but were lower at the end of the trial than at baseline

DOI: 10.3310/hta13010

Trial name	Any AEs and some of the most common	Any SAEs and some of the most common	AEs resulting in temporary or permanent discontinuation	Other notable events
	DFO 40–50 mg/kg/day: any N/R; nausea/vomiting 0/25; skin reactions/allergy 5/25; other N/R	DFO 40–50 mg/kg/day: any N/R; neutropenia 2/28; agranulocytosis 0/28; death 0/28; other N/R	DFO 40–50 mg/kg/day: 3/25	DFO 40–50mg/kg/day: mean ALT levels remained relatively stable
Galanello 2006[97]	Deferiprone 75 mg/kg/day + DFO 30–60 mg/kg/day: any 7/29 (24.1%); vomiting 5/29 (17.2%); abdominal pain 3/29 (10.3%); diarrhoea 1/29 (3.4%); neutropenia 0/29; agranulocytosis 0/29	Deferiprone 75 mg/kg/day + DFO 30–60 mg/kg/day: any N/R	Deferiprone 75 mg/kg/day + DFO 30–60 mg/kg/day: 1/29 (3.4%)	Compared with DFO, no significant change in ALT from baseline to end of the trial for either the combination therapy or DFO groups and no significant difference in trend between the two therapy groups in monthly ALT values
	DFO 30–60 mg/kg/day: any 2/30 (7%); abscess at the site of infusion 1/30 (3.3%); allergic reactions 1/30 (3.3%); neutropenia 1/30 (3.3%); agranulocytosis 0/30	DFO 30–60mg/kg/day: any N/R	DFO 30–60 mg/kg/day: 0/30	
Ha 2006 (well-chelated and poorly-chelated patients)[93]	Deferiprone 75 mg/kg/day or deferiprone 75 mg/kg/day + DFO 30–60 mg/kg/day:[d] any N/R; GI 8/26 (30.8%); ALT increase 6/26 (23.1%); arthropathy 4/28 (15.4%); neutropenia 0/26; agranulocytosis 0/26; other N/R	Deferiprone 75 mg/kg/day or deferiprone 75 mg/kg/day + DFO 30–60 mg/kg/day:[d] any N/R; death 1/26 (3.8%); other N/R	Deferiprone 75 mg/kg/day or deferiprone 75 mg/kg/day + DFO 30–60 mg/kg/day:[d] temporary drug cessation because of ALT increase 4/26	Deferiprone 75 mg/kg/day or deferiprone 75 mg/kg/day + DFO 30–60 mg/kg/day:[d] ALT levels showed marked fluctuation in some patients
	DFO 30–60 mg/kg/day: N/R	DFO 30–60 mg/kg/day: N/R	DFO 30–60 mg/kg/day: N/R	DFO 30–60mg/kg/day: N/R
Tanner 2007[46]	Deferiprone 75 mg/kg/day + DFO 40–0 mg/kg/day: any N/R; GI 12/32 (37.5%); joint problems 3/32 (9.4%); reactions at the drug infusion site 1/32 (3.1%); neutropenia 2/32 (6.3%); agranulocytosis 1/32 (3.1%); other N/R	Deferiprone 75 mg/kg/day + DFO 40–0 mg/kg/day: any N/R	Deferiprone 75 mg/kg/day + DFO 40–0 mg/kg/day: 3/32	Deferiprone 75 mg/kg/day + DFO 40–0 mg/kg/day: any N/R
	DFO 40–50 mg/kg/day + placebo: any N/R; GI 8/33 (24.2%); joint problems 6/33 (5.9%); reactions at the drug infusion site 2/33 (6.1%); neutropenia 0/33; agranulocytosis 0/33; other N/R	DFO 40–50 mg/kg/day + placebo: any N/R	DFO 40–50 mg/kg/day + placebo: 1/33	DFO 40–50 mg/kg/day + placebo: any N/R

AE, adverse events; ALT, alanine aminotransferase; N/R, not reported; SAE, serious adverse events; ULN, upper limit of normal.
a Most of the data are derived from the FDA clinical review[72]
b In Cappellini *et al*.[62] any SAE is reported as deferasirox 0.7% and DFO 1.0%
c In Piga *et al*.[77] abdominal pain is reported as deferasirox 23/48 and DFO 8/23
d Both combination therapy and deferiprone monotherapy are combined with regard to discussion of adverse events in the published papers
e Data provided by the author including data from PowerPoint Presentation[102]

groups receiving combination therapy, all safety and adverse events are discussed below under combination therapy versus DFO or deferiprone.

Combination therapy versus DFO or deferiprone

Although all ten trials that examined deferiprone or combination therapy commented on at least one AE, the consistency or manner in which these were reported was variable.[95,103,104]

Only three trials reported on all AEs,[95,103,104] which in all instances were more common in patients receiving deferiprone or combination therapy, the most common being GI events.[46,70,91,93,94,97] Neutropenia was mentioned as occurring in a minority of patients receiving deferiprone or combination therapy in five trials[46,70,71,94,104] and in patients receiving DFO in two trials.[70,104]

Not all trials provided a comprehensive summary of all SAEs (i.e. they would often only mention the 'most common' SAE rather than report on all events). Deaths were reported in two trials.[70,93]

The number of AEs resulting in discontinuation was generally low, with the exception of the Olivieri and Brittenham trial,[71] in which around one-third (5/15) of deferiprone patients and one-quarter (3/11) of DFO patients withdrew from the study because of AEs.

Some trials reported that ALT levels tended to fluctuate, particularly in patients receiving deferiprone or combination therapy.

Adverse events from longer-term follow-up studies of deferasirox

Longer-term follow-up data of patients receiving deferasirox, found by the additional literature search, were limited to three studies with a median period of up to two and a half years of follow-up, all of which were published as conference abstracts (*Table 11*).[105–107] All of these patients were previously participants in clinical trials, including RCTs described in the review above. Most patients had beta-TM, although one-fifth were suffering from SCD. In a cohort of just over 1000 patients (including over 400 paediatric patients) SAEs were rare in both adults and children.[106,107] In total there were 15 deaths, of which only one (child) was felt to be possibly drug related by an investigator but not by the Program Safety Board. GI disorders and skin rashes were the most common drug-related AEs. Discontinuation of deferasirox because of AEs was relatively uncommon. No notable effects on liver or renal function were noted. In a cohort of 480 patients,[105] progressive creatinine rises were identified, but these were reported as being generally reversible with dose modification/interruption.

More recently we became aware that a further three abstracts were presented to the 49th American Society of Haematology Annual Meeting in December 2007.[108–110] Two of these[108,109] contained data on the same cohort of just over 1000 patients after a further 12 months; no notable differences in adverse events were reported. The other study[110] is an extension of the Vichinsky *et al*.[81] RCT of patients with SCD.[81] The most common AEs were GI and skin rash; there were no significant changes in markers of liver or renal function; no cases of progressive increases in serum creatinine were reported.

However, post-marketing AE data identified cases of fatal, acute, irreversible renal failure and cytopenias (including agranulocytosis and thrombocytopenia).[111] In September 2007 the FDA[112] published more detailed information on these AEs; the most common involved the GI (including hepatic), renal and haematological systems (*Table 12*). Of 115 suspected AEs, 108 reported a serious outcome including death. Some of these records were duplicates, for example the number of deaths was reported to be 19, of which 17 were unduplicated. There were 24 unduplicated reports of hepatic AEs including increased ALT, increased bilirubin, jaundice, ascites, subclinical and clinical hepatitis, liver failure, hepatic encephalopathy and cholecystitis. Reports of renal AEs in 16 patients included renal failure (of which two AEs were fatal), acute renal failure, glomerulonephritis, interstitial nephritis and renal tubulopathy. There were 15 unduplicated reports of haematological AEs included agranulocytosis, neutropenia and thrombocytopenia. It was reported that 'some' of these patients died. In many of these cases the extent to which AEs may be caused by deferasirox is not known. Three patients with hepatic failure had a significant history of hepatic disease and/or use of concomitant medication with known hepatic AEs, four patients with renal AEs had a history of renal disease and 'most' of the patients with haematological AEs had pre-existing haematological disorders that are frequently associated with bone marrow failure.

DOI: 10.3310/hta13010

TABLE 11 *Adverse events reported in the longer-term studies*

Study name	Study population and intervention	Any AEs and some of the most common	Any SAEs and some of the most common	AEs resulting in temporary or permanent discontinuation	Other notable events
Bennett 2006[105]	480 patients who originally had been included in deferasirox trials 387 (80.6%) entered the extension phases and 334 (69.6%) were on treatment at the time of analysis Median follow-up 2.5 years	N/R	N/R	N/R	Creatinine rises > ULN 58/480 (12.1%). Of these: returned to < ULN 42/58 (72.4%); fluctuated around ULN 3/58 (5%); stabilised at slightly > ULN 9/58 (15.5%); missing data 4/58 (7.1%)
Cappellini 2006[106]	1033 patients who had originally been included in deferasirox trials and who had originally received deferasirox (deferasirox group) or DFO (mean dose of 42.2 mg/kg/day) (crossover group): deferasirox group (mean dose 20.5 mg/kg/day) 703; crossover group (mean deferasirox dose 21.0 mg/kg/day) 330 Beta-TM 749 (72.5%); SCD 185 (17.9%); MDS 47 (4.5%); DBA 30 (2.9%); other 22 (2.1%) Children 433 (41.9%); adults 600 (58.1%) Median follow-up 1.5–2.5 years	All N/R Drug-related: nausea 99/1033 (9.6%); diarrhoea 91/1033 (8.8%); abdominal pain 52/1033 (5.0%); upper abdominal pain 44/1033 (4.3%); vomiting 49/1033 (4.7%); skin rash 49/1033 (4.7%); other N/R	All N/R Death 15/1033 (1.5%); other N/R; all deaths considered unrelated to study drug by the Program Safety Board (one was reported as possibly related by an investigator) Drug-related: nausea 2/1033 (0.2%); diarrhoea 2/1033 (0.2%); abdominal pain 4/1033 (0.4%); upper abdominal pain 1/1033 (0.1%); vomiting 1/1033 (0.1%); skin rash 4/1033 (0.4%); other N/R	72/1033 (7.0%)	No progressive creatinine rises; no changes in markers of liver or renal function that were consistently or significantly different from the core study; physical and sexual development proceeded normally in all patients
Piga 2006[107]	433 children who had originally been included in deferasirox trials and who had originally received deferasirox (deferasirox group) or DFO who had switched to it (crossover group): deferasirox group 289 (66.7%); crossover group 144 (33.3%) Age: 2 to < 6 years 70 (16.2%); 6 to < 12 years 192 (44.3%); 12 to < 16 years 171 (39.5%) 392 (90.4%) still on treatment at time of analysis Median follow-up 1.6–2.6 years	All N/R Drug-related: nausea 17/433 (3.9%); diarrhoea 19/433 (4.4%); abdominal pain 17/433 (3.9%); vomiting 19/433 (4.4%); skin rash 24/1033 (5.5%); other N/R	All N/R Death 2/433 (0.5%); other N/R; both deaths were in the deferasirox cohort and considered unrelated to study drug by the Program Safety Board (one was reported as possibly related by an investigator) Drug-related: nausea 0/433; diarrhoea 0/433; abdominal pain 0/433; vomiting 0/433; skin rash 0/433; other N/R	21/433 (4.8%)	No progressive increases in markers of liver or renal function; physical and sexual development proceeded normally in all patients

AE, adverse events; SAE, serious adverse events; N/R, not reported; ULN, upper limits of normal

TABLE 12 *Adverse events received by the FDA between 2 November 2005 and 20 June 2006 (n = 115 reports)*[112]

MedDRA preferred term	Total case/event count
Gastrointestinal	
Increase in ALT	17
Blood bilirubin increased	16
Diarrhea	17
Nausea	16
Renal	
Blood urea increased	14
Blood creatinine increased	17
Renal failure acute	7
Haematological	
Haemoglobin decreased	18
Platelet count decreased	11
Haematocrit decreased	9
Sickle cell anaemia with crisis	7
Other	
Pyrexia	27
Dyspnea	10
Fatigue	10
Rash	9
Dehydration	9
Malaise	8
Asthenia	7

ALT, alanine aminotransferase; MedDRA, Medical Dictionary of Regulatory Activities.

As a result, product labelling has been updated. In addition, the FDA requested health-care professionals to report any SAEs in association with deferasirox therapy (e.g. renal failure and cytopenias).

Other considerations

At the time of the literature search none of the RCTs included in this review presented quality of life (QoL) outcomes. One trial explicitly stated that it attempted to measure QoL but then failed to present any findings.[87] One of the authors involved in this trial was contacted for further information regarding the various published abstracts but failed to respond to our emails.

Eight trials reported on adherence with deferiprone versus DFO or combination therapy versus DFO and/or versus deferiprone.[46,70,71,91,93,94,96,97] It should, however, be noted that RCTs are not ideal for measuring adherence and tend to overestimate this in clinical practice.

In Olivieri and Brittenham[71] adherence in the deferiprone group was measured with computerised bottles and was reported to be significantly better than adherence in the DFO group measured using ambulatory pumps [deferiprone, mean (SD) = 94.9% (1.1%); DFO, mean (SD) = 71.6% (22.5%); $p < 0.005$).

Adherence with the trial treatment was assessed in Maggio *et al.*[91] by counting the pills in each returned bag of deferiprone, by assessing the total dose of DFO consumed each week and by interviewing the patients' relatives. A total of 55 patients in each trial group (deferiprone = 77.5%; DFO = 75.3%) took the prescribed dose of the trial treatment during the trial period and four patients (5.6%) in the deferiprone group and seven (9.6%) in the DFO group took a reduced dose because of low adherence.

In Pennell *et al.*,[94] Tanner *et al.*[46] and Galanello *et al.*,[97] deferiprone adherence was measured using the Medication Event Monitoring System device (Aardex, Zug, Switzerland) and DFO adherence was measured using Crono pumps (supplemented by the use of diary cards and weekly physical examination of infusion sites in Galanello *et al.*). Adherence in Pennell *et al.*[94] was similar between groups ($p = 0.81$) being 94% (SD 5.3%) in the deferiprone group and 93% (SD 9.7%) in the DFO group. Tanner *et al.*[46] also reported similar rates of DFO adherence in the combination therapy and DFO groups (91.4% compared with 92.6%, $p = 0.7$). This trial also compared adherence with deferiprone tablets in the combination therapy group with placebo tablets in the DFO group and reported adherence with placebo to be significantly better than adherence with deferiprone (89.8% compared with 82.4%, $p = 0.04$); no reason is given for this result. In Galanello *et al.*[97] only adherence with DFO is reported and this was reported to be similar in both the combination therapy (96.1%) and DFO monotherapy groups (95.7%).

Mourad *et al.*[96] defined adherence as either 'excellent' (taking over 90% of the recommended doses) or 'good' (75–90% of recommended doses) and reported adherence to be better with

combination therapy [excellent = 10/11 (90.1%)] than with DFO [excellent = 11/14 (78.6%)].

In Ha *et al*.[93] adherence was determined by diary entry and the use of tablets provided between visits and was reported to be 'excellent' in the combination therapy group with 75% of patients being compliant in taking both deferiprone and DFO. Adherence with DFO alone was considered to be 'good' for 60% of patients and 'poor' for 40% of patients; the criteria as to how these terms were defined are not reported.

In Aydinok *et al*.[70] adherence was assessed by adherence to treatment at weeks 12, 26, 38 and 54; adherence was reported to be better with both combination therapy [30/30 (100%)] and with deferiprone monotherapy [26/26 (100%)] than with DFO [22/25 (88.0%)].

Because of the small sample sizes in the above trials all results should be interpreted with extreme caution.

Following the completion of the literature searches a subsequent paper was published by Cappellini *et al*.[113] relating, albeit indirectly, to QoL and adherence. This paper presents findings on patients' experiences of treatment (reported satisfaction, convenience, preferences and willingness to continue trial treatment) from the Cappellini *et al*.[62] trial. In this trial, which excluded patients with previously poor adherence of DFO, at baseline, one-third of patients in both the deferasirox and DFO groups reported that they were dissatisfied with DFO treatment [94/289 (32.5%) and 93/282 (33.0%) respectively] whereas, at the end of the trial, 38.3% (108/282) of patients in the DFO group and 5.9% (17/289) of patients in the deferasirox group were dissatisfied with their respective trial treatment.[113] Similarly, two-thirds of patients in both groups reported that DFO treatment was inconvenient at baseline [198/289 (68.5%) and 193/282 (68.4%) respectively] but, at the end of the trial, 72.7% (205/282) of patients in the DFO group were inconvenienced by DFO compared with 1.0% (3/289) of patients in the deferasirox group. Amongst patients who had experience of using both deferasirox and DFO, at the end of the trial 0.7% (2/289) of patients stated they preferred DFO to deferasirox compared with 96.9% (280/289) of patients who reported that they preferred deferasirox to DFO. Finally, 85.8% (248/289) of patients receiving deferasirox reported that they would be willing to continue trial treatment compared with 13.8% (39/282) of patients receiving DFO ($p < 0.001$), whereas 3.5% (10/289) and 64.5% (182/282) of patients indicated that they would be unwilling to continue their trial treatment with deferasirox and DFO respectively.

Clinical discussion

The aim of this clinical review was to evaluate the effectiveness of a relatively new oral chelator, deferasirox, in the treatment of iron overload due to transfusional haemosiderosis in patients suffering with chronic anaemia. To achieve this comparisons with other iron chelators were necessary, i.e. DFO, deferiprone and combination therapy (deferiprone and DFO).

The range of outcome markers described in the review may be confusing and the different techniques used to measure LIC made meaningful comparisons problematic. Moreover, there was a diversity of inclusion and exclusion criteria, there were different follow-up periods and both the quality of reporting and the methodological quality of the trials were generally poor. Limited availability of information in two trials presented only as conference abstracts made it difficult to assess the methodological quality and extract data.[114,115] Most trials included in the review were small in size with only three[62,81,91] including more than 100 participants; around half of the patients in the review were in the three trials that compared deferasirox with DFO.[62,77,81] As a result it was possible to undertake meta-analyses with data from only a small subset of the papers included in the review and, in most cases, there was evidence of statistical heterogeneity. It is therefore difficult to interpret the results of the review with any certainty.

The largest trial, which was designed to test for non-inferiority of deferasirox compared with DFO (utilising trial-specific measures of 'success' in terms of changes in LIC), included 586 patients and found that, at licensed doses of 20 mg/kg/day or above, deferasirox was not inferior to DFO.[62] However, some patients in the trial (those with baseline LIC < 7 mg Fe/g dw) appeared to be underdosed, particularly in comparison with patients receiving DFO. Thus, the main claim to non-inferiority is based on post hoc subgroup analysis, which raises concern although it is supported by prespecified secondary subgroup analysis which found that, in terms of mean changes in LIC, deferasirox was not inferior to DFO in patients with a baseline LIC ≥ 7 mg Fe/g

dw (i.e. those patients who received deferasirox at a dose of 20 mg/kg/day or above).[72] In the smaller trials of deferiprone versus DFO, deferiprone was less efficacious in reducing LIC levels than DFO; however, a combination of deferiprone and DFO generally produced comparable results between the two chelators. Only two trials compared combination therapy with deferiprone.

Based on individual trial data, including the large Cappellini *et al.* trial,[62] deferasirox and DFO appear to be generally similar in reducing serum ferritin concentrations. Based on both individual trial data and pooled data there are no significant differences between deferiprone monotherapy and DFO, and combination therapy is superior to DFO. Meta-analyses found no significant differences between deferiprone and DFO or combination therapy and DFO at 6 months. However, there was statistical heterogeneity in the deferiprone trials at both follow-up periods and in the combination therapy trials at 12 months; reasons for the heterogeneity are unknown but this could be accounted for by differences in the study populations. In addition, it should be noted that the number of patients included in each of the pooled analyses was still relatively small. Only two trials compared combination therapy with deferiprone and this was over different follow-up periods.

Only two trials[46,94] included in this review measured changes in cardiac T2* (an indirect measure of myocardial iron overload), neither of which considered deferasirox. These show a statistically significant difference in cardiac T2* levels between the treatment arms favouring deferiprone and combination therapy over DFO.

The outcomes measured in these trials are relatively short term and only measure surrogate end points of the real outcomes of clinical importance (e.g. the effects of iron chelation on morbidity including end-organ damage or other toxicity such as cardiac dysfunction and liver fibrosis). Long-term retrospective studies on morbidity and mortality have reported cardiac events and mortality risk to be lower in thalassaemia patients with good adherence to iron chelation therapy and in those treated with deferiprone as opposed to DFO.[116–118] Similar studies have yet to be conducted, or at least published, in patients receiving deferasirox.

The RCTs suggest that generally deferasirox is safe, but post-marketing follow-up data involving patients receiving deferasirox have identified AEs of considerable concern (e.g. fatal, acute, irreversible renal failure and cytopenias).[111,112] It is currently unclear if these AEs are drug related. Thus, further longer-term observational studies are needed. In the meantime the updating of the product labelling for deferasirox to reflect the current information regarding the cases of acute renal failure and cytopenias has been recommended by the FDA.

Only the Cappellini *et al*. trial[62] reported data on QoL; this appeared in a paper identified following the completion of the review.[113] This study reported that patients prefer deferasirox to DFO in terms of reported satisfaction, convenience, preferences and willingness to continue study treatment. QoL as measured by patient perceptions of their treatment is clearly important with regard to adherence.

Adherence with DFO was measured only in the RCTs that considered this as a comparator to deferiprone and/or combination therapy. Although DFO adherence was not as poor in these trials as would be expected from clinical practice,[119] it should be noted that different methods were used for measuring adherence across the trials and that RCTs by their very nature are not the most adequately designed studies for measuring adherence in the real world. Adherence is an important issue because, although trials may suggest that all chelators are reasonably similar in terms of efficacy, in practice lack of adherence to treatment protocols will clearly limit the likelihood of the treatment being effective.[120] Adherence is more likely to be high in children for whom this is the responsibility of the parent. However, during adolescence, when chelation is becoming the patient's (rather then the parent's) responsibility, anecdotal evidence suggests that there can often be disruption of DFO treatment leading to long-term avoidance (UK Thalassaemia Society, 2007, personal communication).

With the exception of one trial of SCD patients,[81] all of the RCTs included patients with thalassaemia (nearly always beta-TM), with no subgroup analyses by underlying disease. Patients with SCD may start blood transfusions later in life and with less frequency than those with beta-TM. Patients with MDS are typically older than those with thalassaemia or SCD, being in their 50s and 60s; in the current review the average age of each trial population was much lower than this. Furthermore, it has been shown in MDS patients that serum ferritin levels in excess of 1.0 mg/l are related

to reduced survival[20] as opposed to 2.5 mg/l in thalassaemia patients.[5]

Recent data from non-RCTs are only partially illuminating. An open-label study[121] reported that deferasirox reduced mean serum ferritin by around 0.8 mg/l at 12 months, with levels still on average 2.6 mg/l; around one-third of patients developed thrombocytopenia but new cytopenias were considered by the authors to be consistent with haematological progression of MDS. A separate prospective trial[122] of patients with MDS ($n = 47$), DBA ($n = 30$) and other rare anaemias ($n = 22$), as well as thalassaemia ($n = 85$), reported mean reductions in LIC in all disease groups from deferasirox (dose depended on baseline LIC as in the large Cappellini *et al*. RCT,[62] with most patients receiving 20–30 mg/kg); mean changes in LIC correlated to changes in serum ferritin, were dose respondent and greatest in the MDS and smallest in the DBA groups. However LIC was measured by a combination of biopsy or SQUID, with around half of all MDS and DBA patients being assessed by SQUID compared with fewer than one-quarter of patients with thalassaemia or other rare anaemias. There were no differences in the most common AEs (GIs, skin rash and non-progressive creatinine increases) across the disease groups although all deaths [5/184 (2.7%)] were reported in MDS and DBA patients; these were not considered to be drug related. There were 9/184 (4.9%) cases of neutropenia, all felt by the investigators to be related to the disease and not the drug; these were more prevalent in non-thalassaemia patients.

All but three RCTs included a mix of children and adults in their patient populations, with no subgroup analyses by age group. There are pharmacokinetics data which demonstrate that children appear to metabolise deferasirox more rapidly than adults.[77,123] This in turn may have implications with regard to both safety and efficacy although the long-term data to date have shown no apparent differences between children and adults with regard to AEs.

A final factor to be considered which may decrease the value of the studies included is publication bias and the fact that most studies in this area were conducted with pharmaceutical company involvement; such studies in the past in other therapeutic areas have been shown to contain a bias towards the drugs of the sponsor.[124,125]

In summary, there is some evidence in the clinical review to support the use of all three iron chelators in people with iron overload but, for reasons discussed above, these must be interpreted with caution. There is a need to strengthen the evidence base with further research of clinical outcomes, particularly cardiac T2* in patients receiving deferasirox.

Chapter 5
Economic review

Introduction

This chapter explores the published literature on the costs and benefits of iron chelation therapy for the treatment of iron overload in chronically transfused patients. The aim of this review was to identify published cost-effectiveness studies of deferasirox versus DFO, deferiprone or placebo; or deferiprone versus DFO (alone or in combination with deferiprone). Because of limitations in the availability of published information (many abstract-only studies) this review is more a descriptive presentation than a critical appraisal.

Identification of studies

Details of the search strategy and the methods for selecting evidence are presented in Chapter 3. A total of 884 records was identified by the search strategy; five were subsequently singled out as pertaining to the economics of chelation therapy and obtained in full text format to facilitate the application of inclusion/exclusion criteria. Of these, four records were selected for inclusion in the review. A further five abstracts were identified from searching conference proceedings [American Hematology Association (AHA) and European Haemotology Association (EHA)] and one full text article was identified from hand-searching activities, equating to a total of 10 articles.[126–135] From this, eight distinct cost-effectiveness studies were identified: one full paper[131] and seven studies in abstract-only form.[126,127,130,132–135]

Quality assessment

Quality assessment of the abstract-only studies would be meaningless because of word limit constraints. Hence, the decision was taken to apply detailed quality assessment criteria to the single full text article only.[131] In general the quality of this study was high (*Table 13*).

Study characteristics

All eight studies undertook a cost–utility analysis, presenting results as cost per quality-adjusted life year (QALY), and all compared deferasirox with DFO (*Table 14*). Four studies considered only beta-TM patients,[130–133] one study considered SCD patients,[126] one study included only MDS patients[127] and two studies considered beta-TM, SCD and MDS patients as a group.[134,135] Only two studies had a UK perspective, three studies had a US perspective and the remaining studies were Canadian, Brazilian and European. The four studies in beta-TM patients adopted a long-term time frame (lifetime/50 years);[130–133] the remaining studies appeared to be of 1 year in duration. All of the studies had industry author affiliations, and there was a large degree of overlap, in terms of both data sources and authors, between many of the studies.

Economic models

In the studies two distinct modelling approaches were adopted: long-term modelling (lifetime) and short-term (1 year) modelling. See *Table 15* for full details of each of the models.

Short term

Four publications presented data from short-term models,[126,127,134,135] although as none of the publications were full text versions the model details were sparse. The abstract presented on MDS patients in the US[127] provided limited specific information about the model. The model focused on QoL and cost issues in the short term (1 year). Issues of adherence, mortality and adverse events were not considered.

Likewise, the abstract presented on SCD patients in the US[126] provided very few details of the economic model utilised. Only costs and QoL were considered in the short term (1 year); adherence, mortality and adverse events were not included.

The two UK abstracts[134,135] were also unable to provide sufficient detail on the modelling methodology; however, it seems likely that they are derived from the same model. This model looked at iron-overloaded beta-TM, SCD and MDS patients as a group. Once again a relatively simple model was developed that considered

TABLE 13 *Quality assessment*

Checklist item		Delea 2007[131]
1.	The research question is stated	✓
2.	The economic importance of the research question is stated	✓
3.	The viewpoint(s) of the analysis are clearly stated and justified	✓
4.	The rationale for choosing the alternative programmes or interventions compared is stated	✓
5.	The alternatives being compared are clearly described	✓
6.	The form of economic evaluation used is stated	✓
7.	The choice of form of economic evaluation is justified	✓
8.	The source(s) of effectiveness estimates used are stated	✓
9.	Details of the design and results of effectiveness study are given	✓/×
10.	Details of the method of synthesis or meta-analysis of estimates are given	N/A
11.	The primary outcome measure(s) for the economic evaluation are clearly stated	✓
12.	Methods to value health states and other benefits are stated	✓/×
13.	Details of the subjects from whom valuations were obtained are given	✓
14.	Productivity changes (if included) are reported separately	N/A
15.	The relevance of productivity changes to the study question is discussed if included	N/A
16.	Quantities of resources are reported separately from their unit costs	×
17.	Methods for the estimation of quantities and unit costs are described	✓
18.	Currency and price data are recorded	✓
19.	Details of currency price adjustments for inflation or currency conversion are given	?
20.	Details of any model used are given	✓
21.	The choice of model used and the key parameters on which it is based are justified	✓
22.	Time horizon of costs and benefits is stated	✓
23.	The discount rate(s) are stated	✓
24.	The choice of rate(s) is justified	✓
25.	An explanation is given if costs or benefits are not discounted	N/A
26.	Details of statistical tests and confidence intervals are given for stochastic data	N/A
27.	The approach to sensitivity analysis is given	✓
28.	The choice of variables for sensitivity analysis is justified	✓
29.	The ranges over which the variables are varied are stated	✓
30.	Relevant alternatives are compared	✓
31.	Incremental analysis is reported	✓
32.	Major outcomes are presented in a disaggregated as well as an aggregated form	✓
33.	The answer to the study question is given	✓
34.	Conclusions follow from the data reported	✓
35.	Conclusions are accompanied by the appropriate caveats	✓

✓, yes; ×, no; ✓/×partially; ?, uncertain; N/A, not applicable.

DOI: 10.3310/hta13010

TABLE 14 *Study characteristics*

Study	Type of evaluation and synthesis	Interventions	Study population	Country	Time period of study	Industry–author affiliation	Publication type
Delea 2007[131]	Cost–utility analysis; results expressed as cost per QALY	DFO Deferasirox	Transfusion-dependent beta-TM patients suffering from iron overload	US	50-year time-frame	Funding provided by Novartis; two authors are employees of Novartis and own stocks/shares in the company, remaining authors have received consulting fees/honoraria from Novartis	Full paper
Delea 2006[130]	Cost–utility analysis; results expressed as cost per QALY	DFO Deferasirox	Transfusion-dependent thalassaemia patients suffering from iron overload	Canada	Lifetime	None declared but Sofrygin and Delea have received consulting fees from Novartis as declared in the full paper[131]	Abstract
Delea 2006[132]	Cost–utility analysis; results expressed as cost per QALY	DFO Deferasirox No chelation	Transfusion-dependent thalassaemia patients suffering from iron overload	Europe	Unclear; lifetime?	None declared but Sofrygin and Delea have received consulting fees from Novartis as declared in the full paper[131]	Abstract
Calebro 2006[133]	Cost–utility analysis; results expressed as cost per QALY	DFO Deferasirox	Transfusion-dependent thalassaemia patients suffering from iron overload	Brazil	Lifetime	Lead author works for Novartis and Sofrygin and Delea have received consulting fees from Novartis as declared in the full paper[131]	Abstract
Delea 2005[127]	Cost–utility analysis; results expressed as cost per QALY	DFO Deferasirox	Transfusion-dependent MDS patients	US	1 year	Two authors employed by Novartis	Abstract
Delea 2005[126]	Cost–utility analysis; results expressed as cost per QALY	DFO Deferasirox	SCD patients receiving frequent transfusions	US	1 year	Two authors employed by Novartis	Abstract
Karnon 2006[134]	Cost–utility analysis; results expressed as cost per QALY	DFO Deferasirox	Transfusion-dependent patients suffering from iron overload (beta-TM, SCD and MDS patients)	UK	1 year	Co-author employed by Novartis	Abstract
Karnon 2007[135]	Cost–utility analysis; results expressed as cost per QALY	DFO Deferasirox	Transfusion-dependent patients suffering from iron overload (beta-TM, SCD and MDS patients)	UK	1 year	Co-author employed by Novartis	Abstract

TABLE 15 *Description of economic models*

Study	Type of model	Perspective	Base-case model parameters	Model assumptions
Delea 2007[131]	Markov model with annual transitions between health states. Three health states defined: alive without cardiac disease; alive with cardiac disease; dead (absorbing state). Model was constructed in Microsoft Excel	US health-care system	Prescribed dose: DFO 47.4 mg/kg/day for 5 days per week; deferasirox 24.6 mg/kg/day every day Adherence: DFO 64%; deferasirox 74% Annual mortality with cardiac disease 16% Utility difference DFO (0.61) vs deferasirox (0.85) –24 Utility difference cardiac disease vs no cardiac disease –15% Costs: DFO US$35.77 per gram; deferasirox US$89.49 per gram; DFO administration US$56 per infusion; treatment of iron overload-related cardiac disease US$14,770	No adverse events. Once patients develop cardiac disease they cannot go back to cardiac disease-free state. Costs of DFO based on branded version, not generic
Delea 2006[130]	Markov model – limited detail	Ontario provincial health-care system	Costs of yearly DFO therapy: C$6000; cost of drugs not stated	Complications of iron overload and adherence factored into analysis – no details provided
Delea 2006[132]	Markov model – limited detail. Model was same as that used in main US study[131] but adapted to European perspective	European health-care systems	Prescribed dose: DFO 47.2 mg/kg; deferasirox 24.6 mg/kg Costs: DFO €15–40 per 2-g vial; deferasirox €40–50 per 1-g vial; DFO administration €10–40 per infusion	Model inputs the same as main US study[131] apart from costs. Patients assumed to be aged 3 years at model entry. Costs of complications not included
Calebro 2006[133]	Decision-analytic model – limited detail	Brazilian health-care system	DFO administration US$195 per month; cost of drugs not stated	No cost of complications of iron overload apart from cardiac disease
Delea 2005[127]	Unclear	US health-care system	Mean patient weight: 70 kg	No difference in adherence – both fully compliant. Adverse effects of chelation therapy not included
Delea 2005[126]	Unclear	US health-care system	Mean patient weight: 52 kg	No difference in adherence – both fully compliant. Adverse effects of chelation therapy not included
Karnon 2006[134]	Unclear	UK NHS	Mean patient weight: 54kg Prescribed dose: DFO 37 mg/kg 236 days per year; deferasirox 20 mg/kg per day Adherence: DFO 83.7%; deferasirox 83.7% Utility difference DFO (0.61) vs deferasirox (0.85) –0.24 Cost: DFO £8.88 per gram; deferasirox £34 per gram	No costs of adverse events or monitoring. No difference in adherence, although both groups assumed to not be fully compliant with therapy
Karnon 2007[135]	Unclear	UK NHS	Mean patient weight: 42 kg Prescribed dose: DFO 35 mg/kg 5–7 times per week; deferasirox 20 mg/kg per day Utility difference DFO (0.66) vs deferasirox (0.84) –0.18	Assumed equivalent, only QoL difference between deferasirox and DFO. Costs and disutility associated with adverse events were incorporated (no details given.) No mention of adherence

C$, Canadian dollars; QoL, quality of life.

only the costs and QoL associated with chelation therapy in the short term (1 year). There were no costs or disutility estimates associated with adverse events nor monitoring costs in the first abstract,[134] although these were included in the subsequent abstract.[135] A number of other parameters also changed between the first and second abstract, most notably the assumption of suboptimal adherence in the first abstract, with no mention of this in its successor.

Long term

The model developed by Delea *et al*.[131] for beta-TM patients in the US is by far the most comprehensively described, no doubt because of the fact that the remaining reports were available in abstract-only form. The model was a three-state Markov model with annual transitions between health states. The three health states were defined as alive with no cardiac disease, alive with cardiac disease, and dead (absorbing state). The model works on the assumption that, in the long term, chelation therapy prevents the development of cardiac disease and hence prevents cardiac-related death. Patients are assumed to have improved adherence with deferasirox regimens compared with DFO regimens (74% versus 64%), which in turn leads to a greater protection against cardiac morbidity and mortality. There is also an assumed benefit in terms of QoL from being cardiac disease free, as well as the benefit of an oral over a subcutaneous regime. However, the model does not include the costs and disutilities associated with adverse events.

There are no details of the models provided in the Canadian,[130] European[132] and Brazilian[133] publications (abstract only), although it seems likely that the model developed in the US for beta-TM patients[131] was subsequently adapted to European, Canadian and Brazilian locations. Hence, presumably the parameters are the same as in the US study apart from differences in resource use and costs.

Costing

The majority of studies expressed costs in US dollars; the remaining studies utilised UK pounds, Canadian dollars and Euros. Only half of the studies provided a price year, which ranged from 2004 to 2006. In the long-term studies, discounting of costs was undertaken using rates appropriate to the country of origin. The price of chelators was presented in only three studies,[131,132,134] all of which were in different currencies making comparison difficult, although the price of deferasirox was consistently greater than that of DFO. None of the studies presented resource use separately from costs, making it impossible to validate the estimated costs (see *Table 16*).

Health outcomes

The incorporation of health outcomes was highly dependent upon the time period chosen for the analysis (see *Table 17*).

Short term

The four short-term studies[126,127,134,135] expressed health outcomes in terms of the QoL benefit of oral chelation with deferasirox compared with infusional DFO. Three of the abstracts appear to be based on the same time trade-off (TTO) study of Australian origin, which was presented as an abstract in 2005[136] and published in full in 2007.[137] It is worth noting that the reported utility values vary slightly and do not necessarily match either of the TTO publications. The TTO study was derived from a community-based sample of 110 healthy participants and appears to be of sound methodology.

The later of the two UK short-term studies[135] utilised data from a UK QoL study (personal communication with authors, July 2007), which is not yet published and hence cannot be verified.

Adherence was factored into the first UK publication,[134] although as the rates were equivalent (for both intervention and comparator) this only has the effect of reducing drug costs and should not impact upon the outcomes.

Long term

The four longer-term studies[130–133] expressed outcomes in terms of morbidity and mortality combined with QoL benefits. Adherence was factored into all of the studies although it is not clear exactly how this was achieved in the three abstracts; presumably they utilised the same methods as in the US study.[131] All of the long-term studies applied discounting, using rates appropriate to the country of origin.

The US Delea *et al*. study[131] calculated adherence rates from published sources and assumption,

TABLE 16 *Cost and resource use*

Study	Currency and year	Discount rate	Price of chelator(s)	Costs	Resource use
Delea 2007[131]	US$ 2006	3%	DFO: US$35.77 per gram; deferasirox: US$89.49 per gram	Costs based on wholesale acquisition costs from the *Red book*.[138] Costs of DFO administration were based on the mean per patient administration cost (US$9286) divided by the number of infusions per year (166, taking into account adherence). Administration costs include all infusion or intravenous services and tests, and were taken from the US health insurance claims database. Costs of cardiac disease based on analysis of 35 frequently transfused thalassaemia patients, of whom 16 had claims for cardiac disease; costs for cardiac disease based on mean cost of these 16 patients. Costs and resources not provided separately	Prescribed doses based on main phase III trial (Cappellini *et al.*[62]); however, there were dosage problems with this trial that led to underdosing in deferasirox arm, which may mean that too low a dose of deferasirox is estimated here. Average weight by age based on a quadratic function fitted to data on thalassaemia patients in clinical trials (unpublished data)
Delea 2006[130]	C$ 2004	5%	Cost of drugs not stated	Costs of deferasirox, DFO and drugs used to treat iron overload complications were based on publicly available sources. Costs of DFO were estimated from five Canadian treatment centres and were comprised of the costs of materials and time spent by pharmacists preparing DFO infusions. No actual costs provided	DFO resource use from five Canadian centres. Unsure about other estimates
Delea 2006[132]	€ (year not stated)	3%	DFO: €15–40 per 2-g vial; deferasirox: €40–50 per 1-g vial	Costs of DFO administration €10–40 per infusion. Costs of complications not included	Unclear, presumably same as US study[131]
Calebro 2006[133]	US$ 2006	3%	Cost of drugs not stated	Costs of deferasirox based on anticipated costs; costs of DFO based on current cost to public payers excluding taxes; neither costs stated. Costs of DFO administration calculated from the patient perspective using the Brasindice table for syringes, needles, scalp and other materials (US$195 per month). Costs and resources not provided separately	Unclear, presumably same as US study[131]
Delea 2005[127]	US$ (year not stated)	NA	Cost of drugs not stated	Costs of generic DFO and anticipated costs of deferasirox based on wholesale acquisition costs – not given. Costs of DFO administration based on analyses of insurance claims data for patients with transfusion-dependent anaemia. Costs and resources not provided separately	Dose of DFO and deferasirox based on phase II study in MDS patients – reference not given. Weight of patients based on data from deferasirox trials in MDS patients
Delea 2005[126]	US$ (year not stated)	NA	Cost of drugs not stated	Costs of generic DFO and anticipated costs of deferasirox based on wholesale acquisition costs – not given. Costs of DFO administration based on analyses of insurance claims data for patients with transfusion-dependent anaemia. Costs and resources not provided separately	Assumed patients would receive same doses of deferasirox and DFO as had been reported to be similarly effective in patients with SCD – no reference given. Average weight of patients based on data from deferasirox clinical trials
Karnon 2006[134]	UK£ (year not stated)	NA	DFO: £8.88 per gram; deferasirox: £34 per gram	Costs of drugs based on unit costs 2004/5. Costs of DFO administration based on study in 29 patients from four UK centres. Costs and resources not provided separately	Prescribed dose of DFO based on study in 29 patients. Unsure of source for deferasirox dose – possibly assumption. Mean patient weight of 54 kg based on study in 29 patients in UK
Karnon 2007[135]	UK£ 2004/2005	NA	Cost of drugs not stated	Drug costs estimated from main phase III trial (Cappellini *et al.*[62]) Costs of DFO administration based on study in 29 patients from four UK centres. Costs and resources not provided separately	Prescribed dose of DFO and deferasirox based on Cappellini *et al.*[62] Mean patient weight of 42 kg based on Cappellini *et al.*[62]

C$, Canadian dollars; NA, not applicable.

DOI: 10.3310/hta13010

TABLE 17 *Health benefits*

Study	Outcomes	Quality of life	Adherence	Discount rate
Delea 2007[131]	Main outcome was cardiac-related death. Cardiac mortality is assumed to be dependent on age and lifetime adherence with chelation therapy. Overall rate of cardiac mortality assumed to be the same for DFO and deferasirox (16%), which comes from a small study in 52 patients (but adherence varies and hence affects lifetime risk of cardiac mortality). Patients without cardiac disease were assumed to have a risk of non-cardiac death equivalent to age-matched general population. It was assumed that the risk function for cardiac disease would be a shifted Weibull function, using survival data from Gabutti and Piga.[1] The result was that the risk of cardiac disease increases by 7.3% for every percentage point decrease in adherence	QoL estimated for DFO and deferasirox and also for cardiac and non-cardiac disease. QoL for DFO vs deferasirox based on a study in 110 patients using TTO technique to determine people's preferences for oral vs subcutaneous iron chelation therapy in a community study in Australia. QoL for cardiac disease based on TTO values for heart failure reported in the Beaver Dam health outcomes study[139]	Used lower estimate of adherence with DFO – 64% from Gabutti and Piga[1] rather than 77% from Arboretti,[139] the largest study. Used a small study of 54 patients taking either deferiprone or DFO to estimate a 16% improved adherence with deferasirox compared with DFO. leading to the estimate of 74% adherence with deferasirox	3%
Delea 2006[130]	Probabilities of complications of iron overload and death by adherence with chelation were estimated from public studies	Utilities based on patient preferences for oral vs infusional chelation therapy, as well as published literature and assumption	Adherence with DFO based on health insurance database claims. Adherence with deferasirox based on study of deferiprone	5%
Delea 2006[132]	Probabilities of complications of iron overload and death by adherence with chelation were estimated from public studies	Utilities based on patient preferences for oral vs infusional chelation therapy	Adherence with DFO based on health insurance database claims. Adherence with deferasirox based on study of deferiprone	3%
Calebro 2006[133]	Probabilities of complications of iron overload and death by adherence with chelation were estimated from public studies	Utilities based on patient preferences for oral (deferiprone) vs infusional chelation therapy (DFO)	Adherence based on US health insurance database claims	3%
Delea 2005[127]	Utility only	Utility for MDS patients receiving transfusions based on published data from patients with anaemia due to metastatic cancer. Utility for differences in DFO vs deferasirox based on a TTO study –presumably Australian TTO study	Full adherence with both drugs assumed	NA
Delea 2005[126]	Utility only	Utilities based on TTO study of patient preferences for oral vs infusional chelation therapy (0.57 DFO and 0.82 deferasirox) – presumably Australian TTO study	Full adherence with both drugs assumed	NA
Karnon 2006[134]	Utility only	Utilities based on De Abreu Lourenco *et al.*[136] (0.61 for DFO and 0.85 for oral chelation)	Adherence with DFO based on a study in 29 patients from four UK centres	Not stated
Karnon 2007[135]	Utility only	QoL for DFO vs deferasirox based on a UK study in 110 patients using TTO technique to determine the preference for oral vs infusional iron chelation therapy	No mention of adherence	NA

NA, not applicable; QoL, quality of life; TTO, time trade-off study.

estimating a superior adherence rate with deferasirox than with DFO. The published adherence studies did not directly compare adherence on deferasirox with that on DFO. Furthermore, the authors chose to use adherence data on DFO from one study only,[1] which was the lower of the two available estimates. The authors justified this choice by stating that physicians generally overestimate adherence, hence the lower estimate reflects clinical practice. It is unclear if the adherence with DFO was based on patients receiving DFO via a traditional pump or a balloon infuser. Information on adherence with deferasirox was not available, hence the results of a small study of adherence with deferiprone were used. This led to an overall difference in adherence of 10% (74% deferasirox, 64% DFO).

Adherence was subsequently linked to risk of cardiovascular disease and ultimately cardiac-related mortality. For each percentage point decrease in adherence, the risk of iron overload-related cardiovascular disease was assumed to increase by 7.3%. Given that there is an adherence differential of 10%, this equates to DFO patients having a 73% increased risk of cardiac disease compared with deferasirox patients. After developing cardiovascular disease the risk of death was estimated to be 16% annually, which is based on a small study[140] in Greek thalassaemia patients.

Patients with cardiac disease were also assumed to have a disutility of 0.15 compared with cardiac disease-free thalassaemia patients based on the Beaver Dam study[141] (0.865 healthy volunteers, $n = 1290$; 0.71 congestive heart failure patients, $n = 28$). Issues of QoL were also factored in to estimate patient preference for oral chelation compared with DFO, using the Australian TTO study.[137]

Results and sensitivity analyses

The results and sensitivity analyses (SA) of the published economic evaluations are presented in *Tables 18* and *19*.

Short term

The short-term studies[126,127,134,135] estimated the incremental costs to be greater with deferasirox than with DFO with the exception of Karnon *et al*.[135] The incremental outcomes ranged from 0.16 to 0.25 QALYs, leading to incremental cost-effectiveness ratios (ICERs) that ranged from US$33,387 to deferasirox dominating DFO. All authors concluded that in the short term deferasirox is cost-effective compared with DFO.

Limited details were provided on the sensitivity analyses undertaken in the short-term studies. The UK studies[134,135] explored assumptions on patient weight, dose of deferasirox, DFO pump/balloon usage and utility. In one-way SA, none of the identified parameters was capable of producing an ICER greater than £30,000 per QALY gained; however, in the multiway SA by Karnon *et al*.,[135] assumptions of patient weight, utility and DFO pump usage in combination increased the ICER to above £30,000 per QALY.

The studies in MDS and SCD patients[126,127] did not present any SA but did discuss the fact that the models were sensitive to assumptions of DFO and deferasirox doses and infusional therapy costs and, in the case of MDS, utility.

Long term

The four long-term studies in beta-TM patients[130–133] estimated total incremental costs of US$126,018, Canadian (C)$130,058, €186,000 and US$90,515, with health benefits ranging from 2.9 to 8.1 QALYs. The resulting ICERs were all within acceptable limits, leading the authors to conclude that deferasirox appears cost-effective compared with DFO in their respective locations.

The US study[131] undertook extensive SA. The willingness to pay (WTP) threshold of $50,000 was exceeded under several assumptions, most notably 100% adherence with deferasirox and no disutility associated with DFO compared with deferasirox. Probabilistic SA indicated that deferasirox was cost-effective compared with DFO in 62% of scenarios at a WTP of $50,000.

The European study[132] did not present specific SA as the entire study was considered a SA. The Canadian study[130] did not present SA results but stated that the model was sensitive to assumptions of DFO costs, infusional costs and utility. The Brazilian study[133] did not provide any details on SA.

Summary

The results of this literature review appear to demonstrate the cost-effectiveness of deferasirox compared with DFO for the treatment of iron

DOI: 10.3310/hta13010

TABLE 18 *Study results*

Study	Incremental costs (per patient per year)	Incremental outcomes (per patient per year)	Cost effectiveness ratios (per patient per year)	Authors' conclusions
Delea 2007[131]	Deferasirox vs DFO: costs of chelation therapy US$313,823; costs of administration –US$179,331; iron-related cardiac disease –US$8474; total costs US$126,018	Deferasirox vs DFO: iron overload-related cardiac disease –4.1% patients; cardiac disease-free LYG 5.4; 1.8 LYG (discounted), 4.5 QALYs (discounted)	Deferasirox vs DFO: US$28,255 cost per QALY	Deferasirox is a cost-effective iron chelator from the US health-care perspective
Delea 2006[130]	Deferasirox vs DFO: total costs C$130,058	Deferasirox vs DFO: 2.9 QALYs (discounted)	Deferasirox vs DFO: C$45,054 cost per QALY	In patients with transfusion-dependent beta-thalassaemia the cost-effectiveness of deferasirox vs DFO is within the range considered acceptable in Canada
Delea 2006[132]	Deferasirox vs no chelation: total costs €186,000–266,000; DFO vs no chelation: total costs €70,000–226,000	Deferasirox vs no chelation: 8.1 QALYs; DFO vs no chelation: 4.1 QALYs	Deferasirox vs no chelation: €28,000–35,000 cost per QALY; DFO vs no chelation: €20,000–63,000 cost per QALY; deferasirox vs DFO: less than €50,000 in all scenarios	Although analyses based on actual prices of deferasirox are necessary, this analysis suggests that deferasirox vs DFO or no chelation is cost-effective in a European setting
Calebro 2006[133]	Deferasirox vs DFO: total costs US$90,515 in DFO-naïve patients	Deferasirox vs DFO: 3.8 QALYs in DFO-naïve patients	Deferasirox vs DFO: US$23,425 cost per QALY in DFO-naïve patients	Deferasirox is a cost-effective strategy in Brazil assuming a threshold of three times the GDP per capita
Delea 2005[127]	Deferasirox vs DFO: total costs US$7679	Deferasirox vs DFO: utility 0.23	Deferasirox vs DFO: US$33,387 cost per QALY	The cost-effectiveness of deferasirox vs DFO in patients with transfusion-dependent MDS is favourable. Results may be conservative as did not take into account adherence or side effects
Delea 2005[126]	Deferasirox vs DFO: total costs US$1486	Deferasirox vs DFO: utility 0.25	Deferasirox vs DFO: US$5944 cost per QALY	In SCD patients receiving frequent transfusions deferasirox vs DFO is highly cost-effective. Results may be conservative as did not take into account adherence or side effects
Karnon 2006[134]	Deferasirox vs DFO: drug costs £7739; administration costs –£7551; total costs £187	Deferasirox vs DFO: utility 0.24	Deferasirox vs DFO: £779 cost per QALY	Deferasirox is extremely cost-effective compared with DFO
Karnon 2007[135]	Deferasirox vs DFO: drug costs £6117; administration costs –£7552; monitoring/AE £19; total costs –£1416	Deferasirox vs DFO: utility 0.164	Deferasirox vs DFO: dominant	Deferasirox dominates DFO

AE, adverse events; C$, Canadian dollars; GDP, gross domestic product, LYG, life-years gained.

TABLE 19 *Study sensitivity analysis*

Study	One-way sensitivity analysis	One-way sensitivity analysis key results	Model drivers	Multiway sensitivity analysis	Probabilistic sensitivity analysis
Delea 2007[131]	One-way SA was performed on adherence with DFO, adherence with deferasirox, annual probability of cardiac disease, increase in risk of cardiac disease per 1% increase in adherence, annual mortality with cardiac disease, daily dose of deferasirox, cost of DFO, cost of deferasirox, cost of DFO administration, annual cost of cardiac disease, disutility for thalassaemia and no chelation, disutility for DFO vs deferasirox, and disutility with cardiac disease	Deferasirox was dominant under the assumption of daily dose of deferasirox set to 12.3 mg/kg/day or when cost of deferasirox was $35.77 per gram Deferasirox exceeded the WTP of US$50,000 under the assumption of adherence with deferasirox 100% or daily dose of deferasirox 36.9 mg/kg/day or cost of DFO US$0 or cost of DFO administration US$0 or disutility for DFO vs deferasirox 0%	One-way SA identified adherence with deferasirox; daily dose of deferasirox; cost of DFO; cost of deferasirox; cost of DFO administration; disutility of DFO vs deferasirox	NA	Deferasirox is preferred to DFO in 62% of simulations when the WTP is US$50,000
Delea 2006[130]	None presented	None presented	Cost-effectiveness was sensitive to cost of DFO and infusional therapy, as well as the QoL of oral vs infusional therapy, and is more favourable in younger patients	None presented	None presented
Delea 2006[132]	Entire paper was a SA				
Calebro 2006[133]	None presented	None presented	Not discussed	None presented	None presented

Study	One-way sensitivity analysis	One-way sensitivity analysis key results	Model drivers	Multiway sensitivity analysis	Probabilistic sensitivity analysis
Delea 2005[127]	None presented	None presented	The ICER was sensitive to assumed dosages of DFO and deferasirox, the cost of infusional therapy and the decrement in QoL associated with transfusional therapy	None presented	None presented
Delea 2005[126]	None presented	None presented	The ICER was sensitive to assumed dosages of DFO and deferasirox and the cost of infusional therapy	None presented	None presented
Karnon 2006[134]	One-way SA performed on mean weight, dose of deferasirox, and utility gain	Weight increased to 70 kg: £10,333 cost per QALY; deferasirox dose 10 mg/kg: deferasirox dominates; deferasirox dose 30 mg/kg: £24,217; utility gain decreased by 50% (0.12): £1559	Not discussed	None presented	None presented
Karnon 2007[135]	One-way SA performed on mean weight and DFO pump/balloon usage	Mean weight increased to 62 kg: £12,566; 50% balloon and 50% pump with DFO: £8017	Not discussed	Multiway SA performed on mean weight and DFO pump usage; DFO pump usage, mean weight and utility gain	Mean weight 62 kg, 50% pump and utility reduced by 25%: £36,311; mean weight 62 kg and 50% pump: £26,348

ICER, incremental cost-effectiveness ratio; NA, not applicable; QoL, quality of life; SA, sensitivity analysis; WTP, willingness to pay.

overload in a number of different patient populations and study locations. However, it must be noted that, because of the large proportion of information that was only available in abstract form, the validity of these studies in terms of data sources, methods and assumptions could not be verified, hence conclusions based on their results must be viewed with caution.

That being said, it was still possible to establish two distinct trends in modelling approaches: long-term and short-term modelling, and identify some of the shortcomings of each of the approaches.

The short-term modelling studies (1 year) in SCD patients, MDS patients and beta-TM, SCD and MDS patients as a composite rely on QoL differences solely. Given the chronic nature of iron overload, a 1-year time frame seems short, especially for SCD and beta-TM patients who can survive for many decades if treated appropriately. However, the authors of the short-term studies defend their choice of time frame by acknowledging the lack of long-term data to inform modelling (particularly in SCD and MDS).

The long-term modelling studies (lifetime) in beta-TM patients rely on a number of assumptions concerning adherence and survival to extrapolate to the long term. Although it is justifiable to attempt to determine the long-term effects of chelation therapy, heavy reliance on inference and assumptions is dubious. Without suitable data to validate these assumptions it is difficult to ascertain the reliability of the cost-effectiveness results.

This literature review highlights the difficulties of matching up the needs of a long-term model that will capture all of the important factors and issues associated with a chronic condition such as iron overload (this is especially complex given the different patient populations) with the constraints of limited data, which is no doubt due to the rarity of iron overload.

Chapter 6
Economic evaluation

The review of the published economic evaluations demonstrates that developing a model for iron-overloaded patients receiving deferasirox is highly complex because of the differing patient populations and the paucity of long-term data. This chapter attempts to build on this knowledge, together with findings from the clinical review. We begin by defining the patient population, health outcomes and costs from an economic perspective. We then describe the development of a limited short-term economic model and present the results obtained.

Health outcomes

Our systematic review of RCT clinical data was unable to discern a statistically and clinically important difference in terms of reductions in LIC and serum ferritin between deferasirox and DFO. Little could be gleaned on the comparative effectiveness of deferasirox and deferiprone because of the lack of data for this comparison; however, it must be acknowledged that the analysis was severely limited by a high degree of heterogeneity between trials and reported outcomes. Nevertheless, although absence of evidence is not evidence of absence,[142] it seems plausible for the purposes of our economic analysis to assume that the three chelators are equivalent in terms of LIC and serum ferritin in the short term (1 year).

It is impossible to use this short-term RCT data to make inferences on long-term health outcomes such as myocardial iron loading, cardiac disease (which is especially important for beta-TM patients) and survival. As deferasirox is a relatively new compound, long-term data from non-RCT sources are not yet available to assess the safety and survival profiles in any patient population. There are some limited survival data from beta-TM patients treated with DFO but how reliable these data are as a proxy for the survival of any patient population treated with deferasirox is questionable. Considering that the adverse event and adherence profiles are known to be different for the two agents, and that the effects of deferasirox on myocardial iron loading and cardiac death in the long term are unknown, making assumptions regarding the long-term benefits of deferasirox seems at best highly speculative and at worst potentially misleading.

Given that it is not possible to determine the long-term health outcomes for patients treated with deferasirox the analysis reduces to a short-term (1 year) assessment. As there is no discernable difference between the three agents in terms of LIC or serum ferritin, the health benefits appear to be restricted to differences in quality of life.

All but one of the published economic evaluations appear to have used the same Australian TTO study[137] to estimate the quality of life gain of oral deferasirox compared with infusional DFO (utility scores of 0.85 and 0.61 respectively). As discussed in Chapter 5, Health outcomes, this study may have a number of problems but in general the methodology was sound and hence the results appear credible. A recent UK study (unpublished), which was used in the recent UK economic evaluation (Karnon *et al.*[135]), verified these results (0.84 deferasirox; 0.66 DFO). Personal communication with Novartis, the manufacturer of deferasirox and DFO (Karen Jewitt, July 2007), confirmed that this study employed the same methodology as the Australian study 'but the vignettes describing the different modes of administration were reviewed by UK clinicians and patients and amended to make sure that they were more relevant to the UK setting. Health states were then elicited using the TTO technique in a cross-section of the UK general population.' Hence, for our analysis we chose to use the UK figures to estimate the utility of deferasirox (0.84) and DFO (0.66).

No data were identified regarding the utility of deferiprone therapy. Assumptions regarding the utility conferred by deferiprone are required; in view of the high degree of uncertainty, the spectrum of utility values (ranging from 0.66 to 0.84) needs to be explored.

Numerous adverse events are associated with chelation therapy. Of the published economic evaluations, the majority did not include the costs and consequences of adverse events. This is no

doubt because of the added complexity of costing and valuing a large number of adverse events, together with the fact that they do not appear to add significantly to the costs or incur large disutilities as demonstrated by those economic evaluations that did include adverse events. However, it is worth noting that none of the economic evaluations considered deferiprone, which has been linked with neutropenia and agranulocytosis, which can incur substantial health costs and disutilities.

For the purposes of our analysis we have not included the costs and health outcomes associated with adverse events. This is primarily because of the inconsistent reporting of adverse events in the trials (see Chapter 4, Combination therapy versus DFO or deferiprone), which makes it almost impossible to estimate the rates of adverse events. Furthermore, it would be difficult to assign disutilities to these adverse events. The end result of including such arbitrary adverse event data would be at best meaningless and at worst misleading. Our decision not to include speculative adverse event data in the model should not greatly alter the results for the comparison of DFO and deferasirox as they do not appear to have major side effects. However, it may affect the results when considering the comparison of deferasirox with deferiprone (because of its link with agranulocytosis), potentially in favour of deferiprone.

Patient populations

Our previous description of the various anaemic conditions that may be at risk of iron overload (see Chapter 2) clearly demonstrates that the different anaemic conditions represent distinct patient populations with regards to aetiology, morbidity and mortality. The strongest evidence of the benefits of chelation therapy comes from patients suffering from beta-TM, followed by SCD patients. There is almost no evidence from MDS patients and very little with regards to other rare anaemias.

Considering that only beta-TM, and to a lesser degree SCD, patients have sufficient evidence of the harms of iron overload and the benefits of chelation therapy, our economic analysis will only consider these two patient populations. Beta-TM and SCD represent distinct populations and may not have the same pattern of organ damage and long-term health benefits (see Chapter 2). However, our short-term model only includes the QoL benefits of oral versus infusional therapy (rather than long-term morbidity and mortality), which should not be dependent on the patient's underlying disease. Therefore, for the purposes of this economic evaluation we will group SCD and beta-TM patients together.

Costs

There are numerous costs associated with iron overload but for the purposes of this review we have only considered those costs borne by the NHS. Hence, only the costs of chelation therapy, monitoring and administration are discussed. As mentioned earlier, adverse events were not included in our analysis.

Monitoring costs

There are a number of monitoring tests that are required when patients receive chelation therapy; however, for the purposes of our economic analysis we have only included the costs of tests that are required in addition to the normal amalgam associated with DFO. During the initial period of treatment tests are required more frequently than during the maintenance period. For the purposes of our analysis the costs of tests have been included for maintenance therapy rather than for the induction phase.

A common consequence of deferasirox treatment is raised creatinine; hence, monthly creatinine tests are required. The price of a serum creatinine test (£12) was obtained from an online laboratory.[143]

Deferiprone has been linked with neutropenia and agranulocytosis; hence, a neutrophil count is required weekly. We were unable to find the price for a neutrophil count hence the price of a complete blood profile (£26) was obtained from an online laboratory.[142] This overestimates the neutrophil monitoring costs associated with deferiprone but is unlikely to bias the results significantly.

Administration costs

Deferiprone and deferasirox are both oral agents and hence will not incur any administration costs. However, DFO is given as an infusion over several hours and will therefore have substantial administration costs. A recent UK study[144] assessing the costs of DFO was undertaken on behalf of Novartis. This study is currently only

available in abstract form and hence does not present individual resource items and unit costs. We contacted Novartis directly (Karen Jewitt, July 2007) and were provided with a table of DFO administration costs broken down into unit costs and resource use. A modified form of this is presented in Appendix 7, split into pump and balloon infuser usage. As can be seen the costs associated with DFO administration are highly dependent on the assumed usage of balloon infusers in place of the traditional pump. In patients who receive DFO via the pump the annual administration costs are in the region £1392, whereas in patients who receive DFO via the balloon infuser the costs are approximately £9179.

It is difficult to obtain an accurate estimate of the proportion of patients receiving DFO via the balloon infuser in clinical practice; furthermore, this information was not available in the UK Thalassaemia Society database that we had access to. Data from Novartis estimate the proportion to be 79%; however, discussions with clinicians indicate that this figure seems high and that the usage of balloon infusers is highly variable and depends on a number of factors, not least of which is the PCT policy. Hence, for our analysis it was not possible to present a single figure and instead we present two scenarios: one in which patients receive DFO via the traditional pump and one in which patients receive it via the balloon infuser; see Appendix 7 for a breakdown of the costs and see the section later in this chapter on Overview of our economic model, Deferasirox versus DFO, for further details of the modelling scenarios.

Costs of chelation therapy

The average per patient cost of chelation therapy is a function of the patient's weight, the average dose and dosing frequency, together with the cost of the chelator itself. To estimate the costs of chelation therapy a number of assumptions regarding half tablets and vial usage had to be made.

First, accepted clinical practice includes the use of half tablets for deferiprone; however, this still leads to difficulties in achieving the correct dosage. We therefore had to make a further assumption that patients would accept a degree of under- and overdosing. For example, patients requiring 375–600 mg would be assumed to take 1×500-mg tablet, whereas patients requiring 625–850 mg would take 1½×500-mg tablets. This amount of under- and overdosing appears quite large; however, discussions with clinicians indicate that this sort of trade-off is common in practice because of the availability of deferiprone in only a 500-mg tablet preparation.

With regards to deferasirox we assumed that the smallest preparation (125 mg) could also be halved. Given the availability of three different tablet formulations this leads to less under- and overdosing than with deferiprone but inevitably some will still occur. For example, patients requiring 480–510 mg will receive 1×500-mg tablet.

DFO is not an oral agent and hence a different set of assumptions need to be made. We did not assume any vial sharing but we did assume that a patient would round their dose to the nearest available formulation and would not open a new vial unless they required more than 100 mg from it. For example, a patient requiring 650–1100 mg would use 2×500-mg vials. Patients will not be overdosed in this instance but may be underdosed by up to 100 mg/kg. This analysis does account for drug wastage as it assumed that once a vial is opened the contents will not be saved for the next dose. This could have the effect of slightly overestimating the drug costs associated with DFO, which could bias results against DFO; however, the effects should be minimal.

Drug costs

Unit costs for each of the chelators were estimated from the March 2007 edition of the BNF.[47] DFO is available in two vial sizes, 500 mg and 2 g, costing £4.26 and £17.05 respectively. Deferasirox is available in three different 28-tablet packs: 125 mg (£117.60), 250 mg (£235.20) and 500 mg (£470.40). Deferiprone is available only in 500 mg/100-tablet packs costing £152.39.

Average dose and dosing frequency

Deferiprone was assumed to be given at a dose of 25 mg/kg three times daily, equating to 1095.75 doses per year (three times daily for 365.25 days).

It is difficult to estimate the average dose of DFO and deferasirox as, unlike deferiprone, a range of doses are available. In the economic evaluation undertaken by Delea *et al*.[131] average doses of DFO (47.4 mg/kg) and deferasirox (24.6 mg/kg) were based on the mean prescribed dosages in the Capellini *et al*. trial;[62] however, the study acknowledged that patients in the deferasirox arm were underdosed, hence doses are not equivalent between treatment arms or reflective of clinical practice. For our analysis we therefore assumed

maximum doses (DFO, 50 mg/kg; deferasirox, 30 mg/kg) as these dosages seem roughly in line with the Capellini *et al*. trial[62] and should not bias in favour of any treatment. The dosing frequency for DFO was estimated to be five times weekly, equating to 260.89 doses per year. Deferasirox is a once-daily treatment, hence patients are assumed to receive 365.25 doses per year.

Patient adherence to therapy is not considered in this analysis. The decision to exclude adherence was primarily due to the fact that, in a short-term model in which only quality of life benefits are considered, the inclusion of adherence would bias the results in favour of the drug with poor adherence (because of the costs being decreased for this agent).

Patient weight

All drug doses are dependent on body weight, hence the choice of weight is crucial when calculating the drug costs. The published economic evaluations described in Chapter 5 estimated body weight to range from 42 kg to 70 kg, which is no doubt a factor of the different patient populations being studied. All of the studies used point estimates for weight, which is not reflective of reality. We wanted to provide a more accurate basis for calculating drug costs and hence decided to calculate weight distributions for both males and females separately, at ages ranging from 2 to 18 years plus.

Weight data were readily available for SCD patients[145] for both males and females ranging from 0 to 18 years of age. The data were only available graphically and had to be digitised to produce the raw weight data, split into males and females. A log-normal distribution was fitted to the male and female data sets for each age. This was used in the model to estimate the average dose required for each sex and age.

Unfortunately weight data were not readily available for beta-TM patients. We therefore assumed that the weight of thalassaemia patients would be equivalent to that of SCD patients at the same age. This may overestimate the weight of beta-TM patients as historically they are generally thought to be smaller and thus lighter than SCD patients because of delayed puberty and growth. However, the majority of this growth dysfunction is thought to be related to poor chelation rather than a factor of beta-TM itself, thus with advancements in chelation therapy there is no reason why these patients should be any shorter/lighter than SCD patients.

Overview of our economic model

We developed a simple 1-year analysis that estimates the costs and benefits of chelation therapy for SCD and beta-TM patients, split into males and females and stratified by age, ranging from 2 to 18 years plus in yearly intervals. The model makes comparisons between deferasirox and DFO and between deferasirox and deferiprone.

The only benefits that could be attributed to the different agents were the utility benefits associated with an oral therapy over infusional chelation therapy. As the analysis was of 1 year in duration only, no discounting was undertaken. The three agents are assumed to be equally effective with regards to removing iron from the body and the analysis does not consider issues of adherence or adverse events.

Only the costs outlined in the previous sections were included in the model. This represents an NHS perspective and, once again, considering the short time frame, it was not appropriate to undertake discounting. All costs are based on 2007 prices apart from DFO administration costs, which are based on 2004/5 prices (Karen Jewitt, Novartis, August 2007, personal communication).

Because of uncertainties regarding the utility associated with deferiprone and the usage of balloon infusers to administer DFO, a range of sensitivity analyses or 'scenarios' are presented rather than a single base case. These scenarios are outlined below, split into two comparisons: deferasirox versus DFO and deferasirox versus deferiprone.

This analysis is highly speculative and, given the dearth of data, must be interpreted with caution. As the results of our model are effectively a range of sensitivity analyses, no separate sensitivity analyses were undertaken.

Deferasirox versus DFO

Because of uncertainty regarding the usage of balloon infusers to administer DFO and any health benefits associated with them, three separate scenarios are presented. All other parameters within the model remain constant and the utility associated with deferasirox is fixed at 0.84. See *Table 20* for a summary of the costs and health outcomes included in the analysis for beta-TM and SCD male patients.

DOI: 10.3310/hta13010

TABLE 20 *Costs and outcomes for deferasirox versus DFO in male beta-TM/SCD patients*

		Deferasirox				DFO			
Age (years)	Mean weight (SD), kg	Annual drug costs (£)	Annual monitoring costs (£)[b]	Total costs (£)	Average utility	Annual drug costs (£)	Annual administration costs (£)[c]	Total costs (£)[c]	Average utility[d]
2	11.1 (1.17)	4250.85	144	4386	0.84	1340.88	1392–9179	2733–10,520	0.66–0.76
3	13.0 (1.35)	4998.43	144	5144	0.84	1963.12	1392–9179	3355–11,142	0.66–0.76
4	14.7 (1.53)	5641.98	144	5766	0.84	2184.32	1392–9179	3577–11,364	0.66–0.76
5	16.2 (1.78)	6208.58	144	6313	0.84	2213.49	1392–9179	3606–11,393	0.66–0.76
6	17.7 (2.03)	6771.21	144	6915	0.84	2241.56	1392–9179	3634–11,421	0.66–0.76
7	19.3 (2.24)	7388.76	144	7533	0.84	2343.64	1392–9179	3736–11,523	0.66–0.76
8	21.2 (2.58)	8087.15	144	8231	0.84	2608.94	1392–9179	4001–11,788	0.66–0.76
9	23.2 (2.91)	8767.77	144	8912	0.84	2924.62	1392–9179	4317–12,104	0.66–0.76
10	25.1 (3.30)	9437.85	144	9603	0.84	3142.51	1392–9179	4535–12,322	0.66–0.76
11	27.2 (3.76)	10,135.74	144	10,280	0.84	3361.40	1392–9179	4754–12,541	0.66–0.76
12	29.4 (4.32)	10,925.85	144	11,070	0.84	3580.51	1392–9179	4973–12,760	0.66–0.76
13	31.8 (5.08)	11,846.42	144	11,990	0.84	3853.29	1392–9179	5246–13,033	0.66–0.76
14	35.2 (6.24)	13,108.87	144	13,253	0.84	4228.82	1392–9179	5621–13,408	0.66–0.76
15	39.2 (7.73)	14,598.77	144	14,743	0.84	4670.84	1392–9179	6063–13,850	0.66–0.76
16	43.3 (8.92)	16,128.18	144	16,272	0.84	5127.24	1392–9179	6519–14,307	0.66–0.76
17	46.8 (9.38)	17,418.84	144	17,563	0.84	5512.97	1392–9179	6905–14,692	0.66–0.76
18+	49.6 (9.10)	18,450.25	144	18,594	0.84	5826.92	1392–9179	7219–15,006	0.66–0.76

a Data fitted to a log-normal distribution to generate mean and standard deviation.
b Based on monthly creatinine tests priced at £12.
c Lower estimate represents 0% balloon infuser usage (all patients on pump) = scenario 1; upper estimate represents 100% balloon infuser usage = scenarios 2 and 3.
d Lower estimate represents utility with pump (scenarios 1 and 2); upper estimate is utility with infuser (scenario 3).

It is worth noting that this simple analysis takes no account of adherence with DFO via the traditional pump, which is alleged to be poor. However, in a 1-year analysis it is difficult to show the effects of adherence as in the short term its only effects are to reduce the costs associated with the agent prescribed to non-compliant patients, which would bias the results in favour of that agent. A long-term time frame would be required to show the impact on morbidity and mortality caused by non-adherence to therapy.

Scenario 1
This comparison considers the cost-effectiveness of deferasirox versus DFO assuming no use of balloon infusers.

Scenario 2
This comparison considers the cost-effectiveness of deferasirox versus DFO assuming 100% use of balloon infusers. No utility benefit is assumed with the balloon infuser compared with the traditional pump; both are assumed to provide a utility score of 0.66. Given that the balloon infuser is associated with improved adherence and acceptance by the patient, this is unlikely to be reflective of reality; however, it was felt important to present such a case and explore differences in utility in scenario 3.

Scenario 3
This comparison once again considers the cost-effectiveness of deferasirox versus DFO assuming 100% use of balloon infusers; however, this time a utility benefit is assumed with the balloon infuser compared with the traditional pump. It is difficult to estimate the utility benefit associated with the infuser compared with the pump; for the purposes of this analysis we assumed a small 0.04 utility benefit resulting in DFO administered via a balloon infuser offering a utility score of 0.7. This is still considerably less than the 0.84 utility associated with deferasirox and may represent a conservative scenario.

Deferasirox versus deferiprone

Because of uncertainty regarding the utility associated with deferiprone, three separate scenarios are presented. All other parameters within the model remain constant and the utility associated with deferasirox is fixed at 0.84. See *Table 21* for a summary of the costs and health outcomes included in the analysis for beta-TM and SCD male patients.

Scenario 1
The utility associated with deferiprone is equivalent to that offered by DFO, i.e. 0.66. This is a worst-case scenario as it is unlikely that an oral agent will confer the same utility as an infusional agent.

Scenario 2
The utility associated with deferiprone is 0.76. This is still a conservative scenario as the utility of deferasirox is 0.84.

Scenario 3
The utility associated with deferiprone is equivalent to that offered by deferasirox, i.e. 0.84. In this scenario it is assumed that even though deferiprone is given thrice daily it confers the same utility as once-daily deferasirox. This in effect represents a best-case scenario.

Results

The results of our economic model are presented below, split into the various scenarios. Note that, because of space constraints and the fact that there was virtually no difference in terms of cost-effectiveness between male and female patients, only the results for male patients are shown. Please also be aware that all results are incremental, which is in line with NICE guidance on performing cost-effectiveness analysis. This means that interventions are compared with the most appropriate 'current treatment' rather than no therapy.

Deferasirox versus DFO
Scenario 1

Table 22 shows the cost-effectiveness results for deferasirox versus DFO assuming that all patients are using the traditional pump to administer DFO, i.e. no balloon infuser usage.

In beta-TM and SCD male patients deferasirox is cost-effective until approximately 6 years of age (ICER below £20,000 cost per QALY); it may possibly be considered cost-effective between the ages of 7 and 10 (ICER £20,000–30,000 cost per QALY); however, after age 10 it is unlikely that deferasirox is cost-effective compared with DFO delivered via the traditional pump (ICER > £30,000 cost per QALY).

Scenario 2
Table 23 shows the cost-effectiveness results for deferasirox versus DFO assuming that all patients

DOI: 10.3310/hta13010

TABLE 21 *Costs and outcomes for deferasirox versus deferiprone in male beta-TM/SCD patients*

		Deferasirox				Deferiprone			
Age (years)	Mean weight (SD) (kg)	Annual drug costs (£)	Annual monitoring costs (£)[b]	Total costs (£)	Average utility	Annual drug costs (£)	Annual monitoring costs (£)[c]	Total costs (£)	Average utility[d]
2	11.1 (1.17)	4250.85	144	4386	0.84	841.65	1352	2194	0.66–0.84
3	13.0 (1.35)	4998.43	144	5144	0.84	1023.86	1352	2376	0.66–0.84
4	14.7 (1.53)	5641.98	144	5766	0.84	1376.57	1352	2729	0.66–0.84
5	16.2 (1.78)	6208.58	144	6313	0.84	1574.89	1352	2927	0.66–0.84
6	17.7 (2.03)	6771.21	144	£6915	0.84	1647.55	1352	3000	0.66–0.84
7	19.3 (2.24)	7388.76	144	7533	0.84	1684.19	1352	3036	0.66–0.84
8	21.2 (2.58)	8087.15	144	8231	0.84	1780.13	1352	3132	0.66–0.84
9	23.2 (2.91)	8767.77	144	8912	0.84	1970.01	1352	3322	0.66–0.84
10	25.1 (3.30)	9437.85	144	9603	0.84	2175.97	1352	3528	0.66–0.84
11	27.2 (3.76)	10,135.74	144	10,280	0.84	2368.21	1352	3720	0.66–0.84
12	29.4 (4.32)	10,925.85	144	11,070	0.84	2538.38	1352	3890	0.66–0.84
13	31.8 (5.08)	11,846.42	144	11,990	0.84	2734.44	1352	4086	0.66–0.84
14	35.2 (6.24)	13,108.87	144	13,253	0.84	3011.76	1352	4364	0.66–0.84
15	39.2 (7.73)	14,598.77	144	14,743	0.84	3343.49	1352	4695	0.66–0.84
16	43.3 (8.92)	16,128.18	144	16,272	0.84	3687.12	1352	5039	0.66–0.84
17	46.8 (9.38)	17,418.84	144	17,563	0.84	3978.66	1352	5331	0.66–0.84
18+	49.6 (9.10)	18,450.25	144	18,594	0.84	4212.68	1352	5565	0.66–0.84

a Data fitted to a log-normal distribution to generate mean and standard deviation.
b Based on monthly creatinine tests priced at £12.
c Based on weekly full blood counts priced at £26.
d The range of utilities represents the different modelling scenarios: lower estimate = scenario 1; upper estimate = scenario 3.

TABLE 22 *Cost-effectiveness of deferasirox versus DFO assuming no balloon infuser usage*

	Beta-TM/SCD males		
Age (years)	**Incremental cost (£)**	**Incremental utility**	**ICER (£)**
2	1662	0.18	9232
3	1787	0.18	9928
4	2209	0.18	12,275
5	2747	0.18	15,260
6	3281	0.18	18,230
7	3797	0.18	21,094
8	4230	0.18	23,500
9	4595	0.18	25,527
10	5047	0.18	28,039
11	5526	0.18	30,701
12	6097	0.18	33,873
13	6745	0.18	37,472
14	7632	0.18	42,399
15	8680	0.18	48,221
16	9753	0.18	54,182
17	10,658	0.18	59,209
18+	11,375	0.18	63,195

TABLE 23 *Cost-effectiveness of deferasirox versus DFO assuming 100% balloon infuser usage but no health benefits of balloon infusers*

	Beta-TM/SCD males		
Age (years)	**Incremental cost (£)**	**Incremental utility**	**ICER (£)**
2	–6125	0.18	DOM
3	–6000	0.18	DOM
4	–5578	0.18	DOM
5	–5040	0.18	DOM
6	–4506	0.18	DOM
7	–3990	0.18	DOM
8	–3557	0.18	DOM
9	–3192	0.18	DOM
10	–2740	0.18	DOM
11	–2261	0.18	DOM
12	–1690	0.18	DOM
13	–1042	0.18	DOM
14	–155	0.18	DOM
15	893	0.18	4959
16	1966	0.18	10,920
17	2871	0.18	15,948
18+	3588	0.18	19,934

DOM, deferasirox dominates DFO, i.e. it is less expensive and more effective.

are using the balloon infuser to administer DFO, i.e. no pump usage.

In beta-TM and SCD male patients, deferasirox dominates DFO until approximately 14 years of age, after which it is cost-effective, maintaining an ICER of below £30,000 for all ages.

Scenario 3

Table 24 shows the cost-effectiveness results for deferasirox versus DFO assuming that all patients are using the balloon infuser to administer DFO, i.e. no pump usage. But in this scenario the balloon infuser is assumed to confer a small utility benefit (+0.04) compared with the traditional pump (utility now 0.7 for balloon infuser).

In beta-TM and SCD male patients, deferasirox dominates DFO until approximately 14 years of age, and after this it is likely to be cost-effective (ICER below £30,000).

Deferasirox versus deferiprone

Scenario 1

Table 25 shows the cost-effectiveness results for deferasirox versus deferiprone assuming that deferiprone only offers the same utility as infusional DFO (0.66).

In beta-TM/SCD male patients, deferasirox is cost-effective until approximately 5 years of age and may possibly be considered cost-effective between the ages of 6 and 8 years. However, after the age of 8 it is unlikely that deferasirox is cost-effective compared with deferiprone.

Scenario 2

Table 26 shows the cost-effectiveness results for deferasirox versus deferiprone assuming that deferiprone gives a utility of 0.76.

In beta-TM and SCD male patients, deferasirox is unlikely to be cost-effective compared with deferiprone.

Scenario 3

Table 27 shows the cost-effectiveness results for deferasirox versus deferiprone assuming that deferiprone offers the same utility as deferasirox.

Under this assumption, deferasirox is not cost-effective compared with deferiprone in any patient group or at any age as it is more expensive and offers no additional health benefits.

Economic discussion

We developed a simple short-term (1 year) model to assess the cost-effectiveness of deferasirox versus DFO and deferasirox versus deferiprone. Because of data constraints a range of cost-effectiveness scenarios are presented rather than a single base case. These scenarios are split into the comparisons of deferasirox versus DFO and deferasirox versus deferiprone.

The model suggests that in the short term deferasirox may be a cost-effective strategy compared with DFO administered via the balloon infuser; however, this is dependent on the benefit conferred by the balloon infuser. If it assumed to offer the same utility as the traditional pump then deferasirox is cost-effective for all ages and both SCD and beta-TM. If the balloon infuser offers more utility than the standard pump then deferasirox may not be cost-effective for adults suffering from SCD.

If DFO is administered via the traditional pump, which is cheaper than the balloon infuser, deferasirox may not be cost-effective once patients reach adolescence. This is simply attributed to the fact that as the patients mature they require more of the drug (as it is dosed according to weight), which increases the costs of deferasirox to a point at which the costs exceed the benefits.

When deferasirox is compared with deferiprone it is a less clear-cut picture and depends upon the utility benefit attributed to deferiprone in relation to deferasirox. However, given the large price differential between deferasirox and deferiprone it is unlikely that deferasirox will be generally cost-effective for the majority of patients (short term). In all scenarios deferasirox appears to be cost-effective only in the youngest patients (as the lower doses required incur less extra cost); for older children and adults in all scenarios deferiprone appears to be economically more attractive.

Taken as a whole the results could be interpreted as indicating that in the short term deferiprone is more cost-effective than deferasirox and deferasirox is more cost-effective than DFO. However, there are a number of issues that must be considered.

We have not attempted to assess the costs and consequences of adverse events in our model. Of the eight published economic analyses, only one study included adverse events. The adverse

TABLE 24 *Cost-effectiveness of deferasirox versus DFO assuming 100% balloon infuser usage and a 0.7 utility benefit with infusers*

	Beta-TM/SCD males		
Age (years)	**Incremental cost (£)**	**Incremental utility**	**ICER (£)**
2	–6125	0.14	DOM
3	–6000	0.14	DOM
4	–5578	0.14	DOM
5	–5040	0.14	DOM
6	–4506	0.14	DOM
7	–3990	0.14	DOM
8	–3557	0.14	DOM
9	–3192	0.14	DOM
10	–2740	0.14	DOM
11	–2261	0.14	DOM
12	–1690	0.14	DOM
13	–1042	0.14	DOM
14	–155	0.14	DOM
15	893	0.14	6376
16	1966	0.14	14,040
17	2871	0.14	20,504
18+	3588	0.14	25,629

TABLE 25 *Cost-effectiveness of deferasirox versus deferiprone assuming deferiprone offers the same utility as DFO (0.66)*

	Beta-TM/SCD males		
Age (years)	**Incremental cost (£)**	**Incremental utility**	**ICER (£)**
2	2200	0.18	12,224
3	2767	0.18	15,374
4	3047	0.18	16,930
5	3420	0.18	18,998
6	3916	0.18	21,754
7	4497	0.18	24,981
8	5099	0.18	28,328
9	5590	0.18	31,054
10	6056	0.18	33,643
11	6560	0.18	36,442
12	7179	0.18	39,886
13	7904	0.18	43,911
14	8889	0.18	49,384
15	10,047	0.18	55,818
16	11,233	0.18	62,406
17	12,232	0.18	67,957
18+	13,030	0.18	72,386

TABLE 26 *Cost-effectiveness of deferasirox versus deferiprone assuming deferiprone offers better utility than DFO (0.76)*

	Beta-TM/SCD males		
Age (years)	**Incremental cost (£)**	**Incremental utility**	**ICER (£)**
2	2200	0.08	27,504
3	2767	0.08	34,591
4	3047	0.08	38,093
5	3420	0.08	42,746
6	3916	0.08	48,946
7	4497	0.08	56,207
8	5099	0.08	63,737
9	5590	0.08	69,872
10	6056	0.08	75,697
11	6560	0.08	81,994
12	7179	0.08	89,743
13	7904	0.08	98,800
14	8889	0.08	111,114
15	10,047	0.08	125,591
16	11,233	0.08	140,413
17	12,232	0.08	152,902
18+	13,030	0.08	162,870

TABLE 27 *Cost-effectiveness of deferasirox versus deferiprone assuming deferiprone offers the same utility as deferasirox (0.84)*

	Beta-TM/SCD males		
Age (years)	**Incremental cost (£)**	**Incremental utility**	**ICER (£)**
2	2200	0.00	Not CE
3	2767	0.00	Not CE
4	3047	0.00	Not CE
5	3420	0.00	Not CE
6	3916	0.00	Not CE
7	4497	0.00	Not CE
8	5099	0.00	Not CE
9	5590	0.00	Not CE
10	6056	0.00	Not CE
11	6560	0.00	Not CE
12	7179	0.00	Not CE
13	7904	0.00	Not CE
14	8889	0.00	Not CE
15	10,047	0.00	Not CE
16	11,233	0.00	Not CE
17	12,232	0.00	Not CE
18+	13,030	0.00	Not CE

Not CE, not cost-effective.

events associated with DFO and deferasirox appear to incur minimal costs (less than £25 for deferasirox and £6 for DFO including monitoring) and have very little impact on utility. However, no studies have attempted to estimate the costs and consequences of adverse events associated with deferiprone. Given that deferiprone has been linked with neutropenia and agranulocytosis, the costs and disutilities associated with deferiprone complications could be expected to be greater than those associated with DFO and deferasirox. This would impact upon the cost-effectiveness of deferiprone and may mean that it is less economically attractive when compared with deferasirox. However, there have been recent warnings that deferasirox may also be associated with neutropenia and agranulocytosis, although this has yet to be confirmed.

A number of other costs were not included in the model or are subject to significant uncertainty. In our costing analysis we chose to take an incremental approach and thus only included the costs that differed between treatment arms. Hence, the total costs borne by the health-care system are likely to have been underestimated for all three agents, although the incremental costs are thought to be accurate within the scope of the analysis.

Furthermore, in our model we chose to take a NHS perspective and therefore only included the costs borne by the health-care system. If a societal perspective were taken, other costs such as patient time and lost earnings would be included. Given the seriousness of the condition these costs are likely to be considerable.

In terms of health benefits our model assumed that, in the short term, benefits would be restricted to quality of life gains. This assumption is based on the findings of our clinical analysis, which was unable to determine a definitive difference between the three iron chelators. However, this does not mean that such a difference does not exist. There is increasing evidence that deferiprone may offer an advantage over DFO in terms of cardiac iron loading. This is especially important for thalassaemia patients as cardiac disease is the leading cause of death in this patient group. However, the crucial factor is to what degree these surrogate outcomes such as liver, serum and cardiac iron translate into long-term outcomes such as morbidity and mortality. Until this is clarified, any small differences between iron chelators in terms of LIC, serum ferritin or cardiac iron cannot be guaranteed to translate into survival benefits. Considering the chronicity of the condition this must be the primary focus for future research.

In conclusion, deferasirox appears to be cost-effective in the short term compared with infusional DFO. However, the model indicates that deferiprone may be more cost-effective than deferasirox, largely because of the high costs of deferasirox in comparison with deferiprone.

However, it cannot be stressed enough that this analysis is exploratory in nature. The appropriateness of deferiprone as a comparator is still controversial because of its side-effect profile, something that was not explored in this analysis. Furthermore, there was a dearth of data, which necessitated a short-term analysis and a number of assumptions. To be able to form more robust conclusions, further research is required regarding:

- the long-term benefits of the three chelators in each patient population
- the costs of the three chelators in the long term
- the adverse event and adherence profiles of the three chelators in the long term.

Chapter 7
Budget impact

This chapter deals with the potential cost implications to the NHS of introducing deferasirox for the treatment of iron overload in beta-TM and SCD patients.

Eligible patient populations

As described in Chapter 2 there are approximately 624 iron-overloaded patients living with beta-TM and 625 iron-overloaded patients suffering from SCD in the UK. Each year there will be an additional 15 cases of iron overload diagnosed in beta-TM patients and 16 cases of iron overload diagnosed in SCD patients. To turn these estimates into useable figures for assessing the budget impact of deferasirox, a number of assumptions must be made.

First, with regards to prevalence estimates, an age distribution needs to be applied to determine the proportion of patients at each age and their associated costs. To determine the age distribution for each disease, data were taken from clinical trials; for beta-TM the Capellini *et al*. trial[73] was used, whereas for SCD the Vichinsky *et al*. trial[81] was employed. A log-normal distribution was fitted to each data set to determine the number of patients at each age group (see Appendix 8). As our model categorises adults as aged 18 years plus, we needed to estimate the proportion of patients in this group. To do this it was simply a case of summing the proportions from 18 to 64 years. For both diseases adults account for approximately half of the total patient population in the RCTs (beta-TM = 49.5%; SCD = 49.6%). Here we have to make the assumption that the RCTs are reflective of clinical practice, which may not be true.

For incidence estimates the age at which patients are diagnosed and treated for iron overload had to be estimated. For the 15 cases of iron-overloaded beta-TM patients it was assumed that they would present at age 2 years. For the 16 cases of iron-overloaded SCD patients it was assumed that they would present at age 4 years. These estimates are taken from analysis of the trial data and also concur with expert opinion.

Costs

The costs used in our model were also used for estimating the budget impact. These costs include the costs of chelation therapy, monitoring and administration. As there is very little difference between male and female patients in terms of costs, the costs for male patients are used. See *Table 20* for an example of the cost estimates for beta-TM and SCD male patients.

Budget impact results

For each condition we present below a range of budget impact assessments. These analyses are exploratory and aim to give an indication of the likely budget impacts rather than precise estimates.

Beta-TM patients

Four different budget impact estimates are presented for the UK prevalent population of beta-TM patients (see *Table 28*). For details of the budget impact for new cases (incidence) see Appendix 9.

Deferasirox versus DFO via pump

In this instance it is assumed that all patients are receiving DFO via the pump and, with the introduction of deferasirox, all patients will switch over to deferasirox. In this case the budget impact is in the region of £5 million per year for beta-TM patients.

In terms of the 15 new cases per year the budget impact is in the region of £33,000 annually.

Deferasirox versus DFO via balloon infuser

In this instance it is assumed that all patients are receiving DFO by the balloon infuser and, with the introduction of deferasirox, all patients will switch over to deferasirox. In this scenario the budget impact is cost saving in the region of £0.3 million per year for beta-TM patients. This indicates that it is cost saving to give patients deferasirox in place of DFO administered via the balloon infuser.

In terms of the 15 new cases per year the budget impact is a cost saving in the region of £92,000 annually when treating new cases with deferasirox

TABLE 28 *Budget impact of deferasirox for beta-TM patients in the UK*

Age (years)	Number of patients	Log-normal distribution (%)	Total costs deferasirox (£)	Total costs DFO pump (£)	Total costs DFO infuser (£)	Total costs deferiprone (£)	Budget impact deferasirox (£)	Budget impact DFO pump (£)	Budget impact DFO infuser (£)	Budget impact deferiprone (£)	Budget impact current practice (£)
2	12	1.99	4386	2725	10,512	2194	54,572	33,907	130,788	27,292	33,907
3	14	2.25	5144	3357	11,144	2376	72,256	47,149	156,529	33,372	47,149
4	18	2.90	5766	3575	11,362	2729	104,187	64,595	205,307	49,306	64,595
5	21	3.33	6313	3605	11,392	2927	131,337	74,996	236,999	60,892	74,996
6	22	3.60	6915	3634	11,421	3000	155,272	81,592	256,440	67,351	81,592
7	23	3.73	7533	3736	11,523	3036	175,287	86,933	268,137	70,652	86,933
8	23	3.76	8231	4001	11,788	3132	193,230	93,929	276,733	73,528	93,929
9	23	3.73	8912	4317	12,104	3322	207,176	100,355	281,384	77,229	100,355
10	23	3.64	9603	4531	12,318	3528	218,188	102,947	279,879	80,160	120,640
11	22	3.53	10,280	4754	12,541	3720	226,118	104,563	275,851	81,831	138,821
12	21	3.39	11,070	4973	12,760	3890	234,087	105,155	269,823	82,267	154,555
13	20	3.24	11,990	5246	13,033	4086	242,490	106,084	263,566	82,643	169,076
14	19	3.09	13,253	5621	13,408	4364	255,333	108,296	258,323	84,073	168,307
15	18	2.93	14,743	6063	13,850	4695	269,804	110,959	253,468	85,931	167,963
16	17	2.78	16,272	6519	14,307	5039	282,258	113,087	248,162	87,409	167,117
17	16	2.63	17,563	6905	14,692	5331	288,289	113,347	241,170	87,501	164,476
18+	309	49.48	18,594	7219	15,006	5565	5,741,459	2,229,103	4,633,555	1,718,241	3,088,712
Total budget impact (£)							***8,851,342***	***3,676,999***	***8,536,114***	***2,849,678***	***4,923,124***
Deferasirox vs DFO pump			5,174,343								
Deferasirox vs DFO infuser			315,227								
Deferasirox vs deferiprone			6,001,664								
Deferasirox vs current practice			3,928,218								

rather than with DFO administered via the balloon infuser.

Deferasirox versus deferiprone
In this scenario it is assumed that all patients are receiving deferiprone and, with the introduction of deferasirox, all patients will switch over to deferasirox. In this case the budget impact is in the region of £6 million per year for beta-TM patients.

In terms of the 15 new cases per year the budget impact is in the region of £25,000 annually.

Deferasirox versus 'current practice'
In this instance we use a more realistic assumption that some patients receive DFO via the pump, some receive DFO via the infuser and some receive deferiprone. The proportions of patients using each chelator at each age were estimated using a data set presented to the WHO in 1999 (Bernadette Modell, June 2007, personal communication) (see Appendix 10 for further details). As this data is almost 10 years old it is likely to underestimate the use of balloon infusers in clinical practice, hence results should be viewed with caution.

In this scenario the budget impact of using deferasirox for all patients in place of current practice is in the region of £4 million per year for beta-TM patients.

It is not possible to present budget impact figures for new cases for this scenario as the data indicate that all patients initially start with DFO administered via a pump (see Appendix 10).

SCD patients

Four different budget impact estimates are presented below for the population of SCD patients (see *Table 29*). For details of the budget impact for new cases (incidence) see Appendix 9.

Deferasirox versus DFO via pump
In this scenario it is assumed that all patients are receiving DFO via the pump and, with the introduction of deferasirox, all patients will switch over to deferasirox. In this case the budget impact is in the region of £5 million per year for SCD patients.

In terms of the 16 new cases per year the budget impact is in the region of £26,000 annually.

Deferasirox versus DFO via balloon infuser
In this instance it is assumed that all patients are receiving DFO via the balloon infuser and, with the introduction of deferasirox, all patients will switch over to deferasirox. In this case the budget impact is in the region of £0.5 million per year for SCD patients.

In terms of the 16 new cases per year the budget impact is a cost saving in the region of £65,000 annually when treating new cases with deferasirox rather than with DFO administered via the balloon infuser.

Deferasirox versus deferiprone
In this scenario it is assumed that all patients are receiving deferiprone and, with the introduction of deferasirox, all patients will switch over to deferasirox. In this instance the budget impact is in the region of £6 million per year for SCD patients.

In terms of the 16 new cases per year the budget impact is in the region of £36,000 annually.

Deferasirox versus 'current practice'
In this instance the more realistic assumption that some patients receive DFO via the pump, some receive DFO via the infuser and patients receive deferiprone is used. The proportions of patients using each chelator at each age were not available for SCD patients. We therefore used the same estimates as for beta-TM patients (see Appendix 10).

In this case the budget impact of using deferasirox for all patients in place of current practice is in the region of £4 million per year for SCD patients.

It is not possible to present budget impact figures for new cases for this scenario as the data indicate that all patients initially start with DFO administered via a pump (see Appendix 10).

Summary

Our exploratory budget impact assessment indicates that deferasirox is likely to cost the NHS in the region of £4 million per year to treat beta-TM patients and £4 million per year to treat SCD patients, assuming that all patients switch to deferasirox (total budget impact = £8 million for both patient groups using current practice scenario). Deferasirox appears particularly attractive compared with DFO administered via a balloon infuser, leading to cost reductions in treating new cases of iron overload (beta-TM and SCD) with deferasirox rather than with DFO via a balloon infuser. Deferasirox is least economically attractive when compared with deferiprone.

TABLE 29 *Budget impact of deferasirox for SCD patients in the UK*

Age (years)	Number of patients	Log-normal distribution (%)	Total costs deferasirox (£)	Total costs DFO pump (£)	Total costs DFO infuser (£)	Total costs deferiprone (£)	Budget impact deferasirox (£)	Budget impact DFO pump (£)	Budget impact DFO infuser (£)	Budget impact deferiprone (£)	Budget impact current practice (£)
2	4	0.58	4395	2733	10,520	2195	15,953	9921	38,188	7966	9921
3	7	1.13	5142	3355	11,142	2375	36,437	23,775	78,951	16,830	23,775
4	12	1.87	5786	3577	11,364	2739	67,645	41,814	132,855	32,017	41,814
5	16	2.55	6353	3606	11,393	2933	101,442	57,579	181,927	46,834	57,579
6	19	3.12	6915	3634	11,421	3000	134,718	70,792	222,495	58,436	70,792
7	22	3.54	7533	3736	11,523	3036	166,477	82,564	254,661	67,101	82,564
8	24	3.82	8231	4001	11,788	3132	196,429	95,485	281,316	74,746	95,485
9	25	3.98	8912	4317	12,104	3322	221,778	107,429	301,217	82,671	107,429
10	25	4.05	9582	4535	12,322	3526	242,433	114,735	311,757	89,216	134,437
11	25	4.04	10,280	4754	12,541	3720	259,477	119,989	316,546	93,904	159,301
12	25	3.97	11,070	4973	12,760	3890	274,786	123,438	316,735	96,570	181,427
13	24	3.86	11,990	5246	13,033	4086	289,477	126,639	314,637	98,656	201,838
14	23	3.72	13,253	5621	13,408	4364	308,509	130,850	312,122	101,582	203,359
15	22	3.57	14,743	6063	13,850	4695	328,672	135,169	308,771	104,680	204,610
16	21	3.40	16,272	6519	14,307	5039	345,554	138,447	303,811	107,010	204,593
17	20	3.22	17,563	6905	14,692	5331	353,744	139,082	295,926	107,368	201,820
18+	310	49.5	18,594	7219	15,006	5565	5,761,143	2,236,745	4,649,441	1,724,132	3,095,728
Total budget impact £							***9,104,674***	***3,754,453***	***8,621,356***	***2,909,719***	***5,076,470***
Deferasirox vs DFO pump			5,350,220								
Deferasirox vs DFO infuser			483,318								
Deferasirox vs deferiprone			6,194,955								
Deferasirox vs current practice			4,024,630								

Chapter 8
Discussion

This review has examined the comparative efficacy and cost-effectiveness of deferasirox versus DFO and deferiprone for the treatment of iron overload in patients suffering from transfusion-dependent anaemia. The report focuses on beta-TM and SCD patients as these are the most frequently studied. The review only considered short-term outcomes because of the relatively recent introduction of deferasirox into US and European markets and the lack of long-term data in any patient population. Given the chronicity of iron overload this limits the value of this review to inform policy decisions regarding the use of iron chelators in clinical practice. However, the review serves as an aid to focus future research in the area.

Our review of the evidence from RCTs indicates that, in the short term, all of the chelators appear to be efficacious in reducing iron in the liver and blood as measured by mean changes in LIC and serum ferritin. Meta-analysis found combination therapy to be statistically superior to DFO monotherapy in reducing mean serum ferritin concentrations over 12 months; however, there are caveats that must be considered when interpreting this clinical evidence.

With the exception of one trial of patients with SCD, all of the RCT evidence is derived from trials of thalassaemia patients. There is currently no RCT evidence of the benefits of chelation therapy in MDS patients and little data on patients with other rare anaemias. This limits the review to patients with beta-TM and SCD.

The methodological quality of the trials was generally poor. The majority of trials were small in size and there were inconsistencies across trials in terms of the inclusion/exclusion criteria and measurement of outcomes (e.g. biopsy and SQUID for LIC) and the length of follow-up. Furthermore, given the chronic nature of iron overload, trials presenting data at 12 months are only able to provide evidence on surrogate, intermediary outcomes and therefore these studies are unable to fully consider important issues around long-term efficacy, safety and adherence.

Considerable difficulties were encountered when interpreting trial data because trials stipulated different inclusion/exclusion criteria with regard to age, LIC and serum ferritin. The review was further hampered by the fact that trial reporting was inconsistent or incomplete (e.g. trials not reporting details of baseline age, LIC or serum ferritin). Differences in the baseline levels that were reported also raised doubts about the validity of pooling data (e.g. when studies included only children or only adults).

With regard to outcome measurement, changes in LIC, serum ferritin and T2* are intermediate, surrogate measurements of long-term morbidity and mortality outcomes, none of which is precise or without bias. Comparing LIC has been particularly problematic as different studies have used different measurement techniques, i.e. invasive biopsy or non-invasive techniques such as SQUID and liver T2*. The validity of non-invasive techniques is yet to be universally accepted. Furthermore, LIC and serum ferritin may not be the best predictors of long-term consequences such as cardiac disease and death. Thus, the development of methods to assess cardiac iron (e.g. T2*) is of paramount importance, particularly for thalassaemia patients; however, the analytical validity of such tests needs further research. Even more crucially, the link between cardiac iron and cardiac morbidity and mortality still needs to be substantiated.

There is evidence that children and adults metabolise deferasirox differently and so efficacy may also differ by age. Unfortunately, none of the RCTs conducted subgroup analysis to address this issue. Further studies that are adequately powered to enable subgroup analysis by paediatric and adult populations would be informative.

Our economic modelling suggests that, compared with DFO, deferasirox may be a cost-effective strategy for beta-TM and SCD patients; however, this is highly dependent upon the age of the patient and the use of balloon infusers to administer DFO. If deferasirox is compared with deferiprone it is likely that deferasirox will be cost-effective only for young children. Furthermore,

if deferiprone is proven to offer the same health benefits as deferasirox, deferasirox will not be cost-effective for any patient compared with deferiprone.

In terms of the financial impact placed upon the NHS by the introduction of deferasirox, our analysis indicates that for both beta-TM and SCD patients the total budget impact is likely to be in the region of £8 million per year. However, this figure is dependent upon the assumed usage of DFO and deferiprone in current practice. Deferasirox is most economically attractive when compared with DFO administered by a balloon infuser and least attractive when compared with deferiprone.

The key issue for any economic evaluation of chelation therapy is the long-term benefit of therapy. Currently, the consequences of iron overload are only understood in thalassaemia patients, and this understanding is imperfect in the long term. Inferences on the effects of iron overload in SCD patients are currently based on the effects of iron in thalassaemia patients, but the two populations are quite dissimilar and hence the effects of iron overload may not be the same.

The effects of iron overload and the benefits of chelation therapy in MDS and other rare anaemias are currently not known. MDS patients are potentially the largest patient group at risk of iron overload, although, considering that MDS patients are older than SCD and beta-TM patients, the benefits of chelation therapy, in terms of morbidity and mortality, are likely to be different. Until these benefits are elucidated it is impossible to determine the clinical effectiveness and cost-effectiveness of chelation therapy in MDS patients. Likewise, there are many other rare anaemias, such as Diamond Blackfan, for which the benefits of chelation therapy require further elucidation.

Two further issues, which are intrinsically linked to the long-term health benefits of chelation therapy, are adherence to therapy and adverse events. The problem of non-adherence to chelation therapy has been well documented in the literature, most notably with the infusional agent DFO. Indeed, the major driving force behind the development of deferasirox was to promote adherence by developing an oral formulation. The health benefits offered by a treatment will not be conferred to patients if they do not actually take it. This is an important issue for these patients as there is growing evidence that non-adherence to therapy leads to reduced life expectancy in thalassaemia patients.[6] It is difficult to accurately estimate the impact of non-adherence on the health benefits conferred by chelation therapy, as the long-term benefits of chelation therapy are difficult to quantify. Moreover, adherence to therapy is not a simple binary variable but represents a spectrum of drug-taking behaviours. Hence, formally valuing the effects of non-adherence to therapy and incorporating it into an economic evaluation is complex.

Long-term adverse events of chelation therapy impact upon the health outcomes and may also impact upon adherence. As deferasirox is relatively new the long-term adverse events are not known and will be identified only by postmarketing surveillance studies in clinical practice.

All of the above issues relate to long-term outcomes, which will take many years to unfold. However, considering the limited patient numbers involved it seems feasible to set up long-term databases which will ensure the collection of accurate data that can be used in the future to assess the long-term clinical effectiveness and cost-effectiveness of chelation therapy. Until quite recently (2003) a large database of virtually all UK thalassaemia patients existed (UK Thalassaemia Society database). If practical, a similar database for all patients receiving chelation therapy (or different databases by underlying disease) would enable long-term health outcomes to be captured.

The costs of chelation therapy must also be considered and include the costs of the chelators, the costs of administration (DFO only), the costs of monitoring and the costs of treating adverse events. Doses for all three chelator agents are based on body weight; hence, it is important to accurately estimate a patient's weight, which will be dependent on the underlying disease, age and sex. Weight curves for each population could be produced according to age and sex. The collection of actual patient weight data directly from clinical practice would be desirable and would increase the accuracy of any economic evaluation undertaken in this area.

The costs of DFO administration are composed of a number of resources. By far the largest cost is attributed to the use of balloon infusers over traditional pumps. Currently the only data available comes from a small, company-sponsored study, which estimates that 79% of patients receive DFO via the balloon infuser. Our clinical panel

indicated that this figure appeared high, although it may be appropriate for certain patients in particular geographic locations. Considering that this is a major component of the costs of DFO it is crucial to estimate the true usage of balloon infusers. It would also be useful to know the benefits of balloon infusers over the traditional pump. If patients prefer balloon infusers to pumps it seems reasonable to assume that there must be some benefit in terms of quality of life and/or adherence to therapy, both of which will impact upon long-term outcomes.

The costs of monitoring also require clarification. The summary of product characteristics (SPC) for the three agents recommend a host of monitoring tests, some generic to iron chelation therapy, others specific to the individual agents. Discussions with clinicians indicate that these tests can often be performed at the same time, which may not be in accordance with the SPC; furthermore, different treatment centres may have different practices. It would be expedient to have these costs more clearly defined and any differences between treatment centres identified.

Finally, the costs associated with adverse events need to be determined. Discussions with clinicians indicate that different treatment centres have different policies with regards to treating patients suffering from an adverse event. For adverse events to be incorporated into an economic evaluation some consensus on their treatment would be required.

Chapter 9

Conclusions and research recommendations

This review indicates that, in the short term, the currently available chelators are effective at removing iron from the body. In addition, deferasirox is potentially cost-effective compared with DFO in SCD and beta-TM patients but it is unlikely to be cost-effective compared with deferiprone in these groups. This review was unable to assess the efficacy and cost-effectiveness of deferasirox for patients with MDS and other rare anaemias.

Our clinical and economic analyses were restricted by the available evidence and thus should be considered exploratory. Our review raises a number of issues that can be used to direct future research in this area, ranked in order of importance (note that this is of importance from the perspective of the researcher and not from that of the NHS or clinician):

- Accurate data must be captured from longer-term use of chelating agents, such as adverse events, adherence, morbidity and mortality. One means to achieve this could be by the establishment of a database for all patients receiving chelation therapy.
- Further research is required to validate new diagnostic tools, such as T2* against cardiac iron, and to establish the link between cardiac iron and longer-term outcomes, such as cardiac morbidity and mortality.
- To ensure comparability across trials in this area, the conduct and reporting of trials need to be consistent. This requires the utilisation of appropriate inclusion and exclusion criteria and adequate reporting of baseline characteristics and deviations from drug-dosing algorithms.
- When trials include a mix of age groups and diseases, they should be adequately powered to allow for subgroup analyses by age and underlying disease. Alternatively, trials will be needed for specific age and disease groups. In particular, clinical studies (including RCTs) are required to establish the clinical effectiveness of deferasirox in patients with MDS and other rare anaemias.
- Costing iron overload and chelation therapy is complex. There is a need for independent costing studies to be undertaken to collect data (including patient weight, proportion of balloon infusers, monitoring tests and adverse events costs) from a variety of patient populations and treatment centres.

Acknowledgements

The review team is pleased to acknowledge Dr Christos Sotirelis, Vice-President of the UK Thalassaemia Society, who provided comments on a draft version of our report; Ms Janet Atkinson who provided administrative support (including obtaining bibliographic sources); Karen Jewitt, Andy Jones and Nan Oliver from Novartis Pharmaceuticals UK Limited, who answered queries and supplied costing data and information regarding recent trials; Dr Alan Haycox and Dr Ruben Mujica-Mota who provided comments on the economic modelling.

Three referees considered and commented on the final version of this report post submission. The policy of NCCHTA is not to name referees; however, individuals contributing peer review of HTA Programme products are listed within the NCCHTA website (www.ncchta.org).

This report was commissioned by the NHS R&D HTA programme on behalf of the National Co-ordinating Centre for Health Technology Assessment and was produced by the Liverpool Reviews and Implementation Group (LR*i*G). The LR*i*G was established at the University of Liverpool in April 2001. It is a multidisciplinary research group whose purpose, in the first instance, is to conduct Health Technology Assessments (HTA) commissioned by the National Institute for Health Research HTA Programme. The views expressed in this publication are those of the authors and not necessarily those of the clinical advisors, the HTA Programme or the Department of Health.

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Professor Adrian Bagust developed the economic model and had input into all aspects of the economic review. Angela Boland, Research Fellow, was responsible for the economic review and writing and editing of drafts of the report. Patrick Chu, Consultant Haematologist, had input into the clinical component of the review. Rumona Dickson, Director, Lr*i*G, had input into all aspects of the clinical component of the review. Yenal Dundar, Research Fellow, was responsible for development of search strategiesa and study selection and had input into aspects of the clinical component of the review. Nigel Fleeman, Research Fellow, was responsible for data management and had input into all aspects of the clinical review. Janette Greenhalgh, Research Fellow, had into all aspects of the clinical review. Jamie Kirkham, Research Associate, was responsible for statistical advice and meta-analysis and had input into all aspects of the clinical review. Claire McLeod, Research Fellow, wa sresponsible for co-ordination of the review and the background, economic review and development of the economic model. Bernadette Modell, Emeritus Professor of Community Genetics, Ade Olujohungbe, Consultant Haematologist, and Paul Telfer, Senior Lecturer in Haematology, all had input into the clinical component of the review, and Bernadette Modell and Paul Telfer wrote the background. Professor Tom Walley was responsible for data assessment and interpretation of clinical data. All contributors took part in the editing and production of the final report.

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Appendix 1

WHO myelodysplastic syndrome classification scheme

Disease	Blood findings	Bone marrow findings
Refractory anaemia (RA)	Anaemia	Erythroid dysplasia only
	No or rare blasts	< 5% blasts
		< 15% ringed sideroblasts
Refractory anaemia with ringed sideroblasts (RARS)	Anaemia	Erythroid dysplasia only
	No blasts	≥ 5% ringed sideroblasts
		< 5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias (bicytopenia or pancytopenia)	Dysplasia in ≥ 10% of cells in two or more myeloid cell lines
	No or rare blasts	< 5% blasts in marrow
	No Auer rods	No Auer rods
	$< 1 \times 10^9$/l monocytes	< 15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Cytopenias (bicytopenia or pancytopenia)	Dysplasia in ≥ 10% of cells in two or more myeloid cell lines
	No or rare blasts	≥ 15% ringed sideroblasts
	No Auer rods	< 5% blasts
	$< 1 \times 10^9$/l monocytes	No Auer rods
Refractory anaemia with excess blasts-1 (RAEB-1)	Cytopenias	Unilineage or multilineage dysplasia
	< 5% blasts	5–9% blasts
	No Auer rods	No Auer rods
	$< 1 \times 10^9$/l monocytes	
Refractory anaemia with excess blasts-2 (RAEB-2)	Cytopenias	Unilineage or multilineage dysplasia
	5–19% blasts	10–19% blasts
	Auer rods ±	Auer rods ±
	$< 1 \times 10^9$/l monocytes	
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias	Unilineage dysplasia in granulocytes or megakaryocytes
	No or rare blasts	< 5% blasts
	No Auer rods	No Auer rods
MDS associated with isolated del(5q)	Anaemia	Normal to increased megakaryocytes with hypolobated nuclei
	< 5% blasts	< 5% blasts
	Platelets normal or increased	No Auer rods
		Isolated del(5q)

Appendix 2

Suggested criteria for the use of deferasirox

Introduction

Effective iron chelation is vital to prevent morbidity and early mortality from the toxic effects of transfusion iron overload. The licensing of a new oral once-daily iron chelator drug deferasirox (Exjade) in the EU earlier this year represents a major advance in chelation therapy, as there were significant problems with adherence and toxic side effects with the previously available chelators desferrioxamine and deferiprone.

Clinical trials with deferasirox have been carried out in the following groups of transfusion-dependent patients and have included children as young as 2 years of age:

- thalassaemia patients
- sickle cell disease patients
- patients with other inherited red cell disorders
- patients with myelodysplastic syndromes.

Iron chelation therapy is required by an increasing number of adults and children treated in the paediatric and adult haematology departments within Barts and The London NHS Trust. The reasons for the increased demand include:

- new indications for transfusion treatment in sickle cell anaemia (mostly for stroke prevention)
- recommendations about chelation therapy in the national standards of care of thalassaemia and for sickle cell diseases, both documents recently published
- increasing numbers of patients, partly as a result of referrals to the Royal London Hospital of patients from elsewhere in East London and Essex after the establishment of the East London and Essex Clinical Haemoglobinopathy Network.

The Barts and The London NHS Trust New Drugs Group has recently considered an application for the use of deferasirox within the trust (25 September 2006).

Based on the recommendations of the New Drugs Group, below are some suggested guidelines for the use of deferasirox. National guidelines are being considered by the UK Forum on Haemoglobin Disorders and local guidelines will then require revision. It seems unlikely that NICE will develop guidelines for iron chelation during the next year.

Suggested guidelines for use of deferasirox (Exjade) for iron chelation therapy in transfusion-dependent patients managed in the East London and Essex Clinical Haemoglobinopathy Network

General considerations

Decisions about chelation should be made by a consultant haematologist experienced in the use of all chelation regimes.

All patients require careful monitoring:

- monthly biochemistry (creatinine, liver function tests)
- 3-monthly clinic visits and serum ferritin
- annual audiometry and ophthalmology, T2* MRI (patients over 10 years)
- additionally, patients on deferiprone require careful monitoring of neutrophil counts (preferably weekly), education about the risk of agranulocytosis and a letter to present in A&E if unwell with fever.

Guidelines for new (previously untreated) patients

Chelation therapy should be considered in children aged over 2 years and in adults who have had at least 1 year of regular transfusions (> 10 transfusions) and who have evidence of iron overload (serum ferritin > 1000 µmol/l on at least two readings separated by 1 month).

Age 2–5 years

Deferasirox is not currently licensed as first-line therapy in this age range. Initial therapy should be with desferrioxamine:

- initiate with desferrioxamine 25 mg/kg subcutaneous infusion five times per week (usually started at two times per week and increased to five times per week over first year of therapy)

- infusions given over 10 hours using either a syringe driver pump (preferably Crono) or a disposable daily infusor pump [advice about desferrioxamine infusions from Dr Telfer (Consultant Haematologist, Royal London Hospital) and Kim Newell (Paediatric Haematology Nurse Specialist, Royal London Hospital)]
- review therapy 3 monthly
- switch to deferasirox (Exjade) if intolerant of desferrioxamine or poor response (increasing serum ferritin); dosage of deferasirox is 20–30 mg/kg per day, initial dose determined by transfusion requirements over previous year and degree of iron overload.

Age 5–16 years
Deferasirox can be given as first-line therapy in this age range. Dosage of deferasirox is 20–30 mg/kg per day, initial dose determined by transfusion requirements over previous year and degree of iron overload.

Adults
First-line therapy is desferrioxamine 30–50 mg/kg, five to six infusions per week using disposable infusors. Deferasirox 20–30 mg/kg should be used as second-line therapy in patients unable to tolerate desferrioxamine as recommended or with severe adverse effects (ototoxiticy, retinal toxicity, *Yersinia* or *Klebsiella* infection).

Guidelines for patients already on chelation therapy
Children aged 5–16 years
Recommend change to deferasirox. Exceptions:

- prefers to stay on desferrioxamine and control of iron load acceptable: stay on desferrioxamine
- cardiac complications or significant cardiac iron loading on T2* MRI: recommend deferiprone alone or in combination with desferrioxamine.

Adults

- If tolerating desferrioxamine well it is not necessary to change chelation.
- If not tolerating desferrioxamine, and normal cardiac status, change to deferasirox.
- If not tolerating desferrioxamine and/or abnormal cardiac function with cardiac iron loading, recommend deferiprone alone or in combination with desferrioxamine.

Exclusions

- Age under 2 years.
- Pre-existing renal disease.
- Pre-existing liver disease (the use in patients with chronic hepatitis C virus infection is currently unclear).
- Severe hearing loss.
- Pregnancy.

Deferasirox (Exjade) therapy: pre-treatment assessment
Before starting treatment the following medical assessment should be carried out:

- height, weight, sitting height
- Tanner staging (age > 12 years)
- general physical examination
- blood transfusion volume over past 12 months (ml/kg)
- urinalysis
- serum creatinine
- liver function tests, including ALT
- serum ferritin
- pure tone audiometry to exclude sensorineural hearing loss
- ophthalmological examination to exclude retinal disease and cataract
- T2* MRI of heart and liver (in patients > 6 years).

Deferasirox (Exjade) therapy: dosage
Initial dose (mg/kg) is based on transfusion requirements during previous 12 months and degree of pre-existing iron overload (*Table 30*).

TABLE 30 *Deferasirox dosage*

Transfusion rate of packed red cells per month	Goal of therapy	
	Maintain iron balance	Reduce iron burden
< 7 ml/kg	10 mg/kg	20 mg/kg
7–14 ml/kg	20 mg/kg	20 mg/kg
> 14 ml/kg	20 mg/kg	30 mg/kg

Deferasirox (Exjade) therapy: monitoring

Weekly for first month of therapy:

- serum biochemistry to include creatinine and liver function tests.

Monthly:

- serum biochemistry to include creatinine and liver function tests
- serum ferritin
- urinalysis for proteinuria.

Annually:

- height, weight, sitting height (age < 20 years)
- Tanner staging (age > 12 years)
- general physical examination
- blood transfusion volume over past 12 months (ml/kg)
- urinalysis for proteinuria
- serum creatinine
- liver function tests, including ALT
- serum ferritin
- pure tone audiometry to exclude sensorineural hearing loss
- ophthalmological examination to exclude retinal disease and cataract
- T2* MRI of heart and liver (in patients > 6 years)
- additional routine annual investigations.

Deferasirox (Exjade) therapy: dose adjustment

Adverse effects

Adjustments can be made every 3 months in 5–10 mg/kg increments.

Increase in serum creatinine: if increased > 1.5 times baseline level or above upper limit of normal (*Table 31*), reduce dose of deferasirox by 10 mg/kg and repeat after 2 weeks. Discontinue deferasirox if elevation persists. Dose can be increased (in 5 mg/kg increments) if creatinine stable at < 1.5 times baseline for 1 month (*Paediatric Laboratory Handbook*, Barts and The London, Division of Blood Sciences; reviewed 1 August 2006).

- Skin rash: this usually resolves without requiring dose reduction. If rash is severe or persisting, discontinue until rash settles and consider rechallenge.

TABLE 31 *Normal serum creatine levels*

Age range (years)	Normal range for creatinine (μmol/l)
1–3	21–36
3–5	27–42
5–7	28–52
7–9	35–53
9–13	46–70
13–15	55–77
Adult	Male 62–106; female 44–80

- Elevated liver aminotransferases (> 2.5 times upper limit of normal): discontinue deferasirox. Monitor weekly with clinical examination and liver function tests. Consider rechallenge at reduced dosage when aminotransferase levels return to normal.
- Hearing loss on pure tone audiometry or symptoms of hearing loss/tinnitus: discontinue deferasirox. Monitor symptoms and audiometry every 1–2 months. Consider rechallenge at a dose 10 mg/kg lower if symptoms and/or audiology findings resolve.

Increasing iron stores

This is indicated by:

- the trend of increasing serum ferritin levels (> 1500 μg/l)
- increasing liver or cardiac loading on T2* MRI scan
- the development of clinical complications of iron overload such as diabetes, cardiac complications.

Increase dose by 10 mg/kg every 3 months. Maximum dose is 30 mg/kg although there is some experience with use at 40 mg/kg. The higher dose should be used only under exceptional circumstances. In general, patients with a high and increasing iron burden should be transferred onto combination chelation therapy with desferrioxamine and deferiprone (see separate protocol)

Diminishing iron stores

In general, the dosage recommended for maintaining iron balance (*Table 30*) should be used. Interruption of treatment should be considered if serum ferritin falls consistently below 500 μg/l.

Appendix 3

Previous systematic reviews of iron chelators

Study	Objective and patient population	Outcomes measured	Studies included	Patients included	Findings and conclusions
Addis 1999[55]	To summarise efficacy in iron-overloaded patients (including thalassaemia, MDS and other anaemias) treated with deferiprone	Proportion of patients whose UIE is ≥ 25 mg/24 hours or ≥ 0.5 mg/kg over the period of treatment; changes in serum ferritin	Nine cohort studies. All studies were published between 1992 and 1995	51 patients in 6/9 studies that reported UIE data and 45 patients from 4/9 studies for which there were data on serum ferritin before and after receiving deferiprone	51.8% of all patients achieved negative iron balance when given a deferiprone dose ≥ 75 mg/kg (45.1% overall regardless of dose) and 75.5% of all patients had a reduction in serum ferritin (average 23.5% drop from baseline)
Caro 2002[57]	Mata-analysis of the literature to assess the effectiveness of deferiprone and DFO in reducing HIC in thalassaemia patients	Change in LIC	11 studies including RCTs ($n = 1$), clinical trials ($n = 5$) and case studies ($n = 5$). All studies were published between 1979 and 1999	98 patients were included in the meta-analysis from 8/11 studies for which there was IPD. All patients were treated with deferiprone ($n = 68$) or DFO ($n = 30$)	DFO was more effective than deferiprone in reducing LIC (OR = 19.0; 95% CI 2.4–151.4)
Malaysian Health Technology Assessment Unit 2003[146]	To determine the safety, effectiveness and cost implications as well as the ethical, legal and social implications of the management of thalassaemia	In relation to chelation therapy, outcomes considered narratively included: morbidity, mortality, safety, complications, changes in serum ferritin and cost-effectiveness	In relation to chelation therapy, 22 studies examining DFO and 13 studying deferiprone. Studies utilised a wide range of study designs including case reports, case studies, cohort studies, case–control studies, surveys, small clinical trials and one meta-analysis.[55] All papers were published between 1983 and 2002	All patients had thalassaemia. The number of patients included in the review is unknown and varied depending on the outcome being considered	DFO and deferiprone are safe and effective and should be used to prevent or improve serious complications of thalassaemia. Combination therapy should be considered in patients with inadequate doses of DFO because of its high cost or side effects
Franchini 2004[58]	To present the main recent developments in iron-chelating therapy in terms of a new method of administering DFO (bolus injections) and two oral chelators (deferiprone and deferasirox)	Narratively: efficacy and safety Meta-analysed: serum ferritin and the following common adverse events: gastrointestinal symptoms, arthropathy, neutropenia, agranulocytosis, hepatoxicity	15 studies including two RCTs. All papers were published between 1990 and 2003	Patients requiring multiple blood transfusions; 1138 patients were included in the meta-analysis	Further studies are needed into the safety of bolus injections and deferasirox; deferasirox results are nevertheless promising regarding future clinical practice. Deferiprone is efficacious and generally well tolerated and is the only oral chelator currently registered for clinical use

DOI: 10.3310/hta13010

Study	Objective and patient population	Outcomes measured	Studies included	Patients included	Findings and conclusions
Roberts 2005[61]	To determine the effectiveness of DFO in people with transfusion-dependent thalassaemia	Mortality (primary outcome) and morbidity (reduced end-organ damage), measures of iron overload including changes in serum ferritin and LIC, adverse events, adherence with DFO and cost of treatment	Overall, eight trials were included examining DFO vs placebo, DFO vs other iron chelators, and different DFO schedules – in terms of DFO vs another iron chelator there were five trials (including one crossover trial). All studies were published between 1974 and 2004 (or 1990 and 2004 for comparisons of DFO with other iron chelators)	All patients had transfusion-dependent thalassaemia and 334 people from eight trials were included in the full review. For DFO vs deferiprone, 144 patients (DFO = 73; deferiprone = 71), all from one RCT, were included in the quantitative analysis of serum ferritin and adverse events and 73 patients (DFO = 33; deferiprone = 40), from two trials, were included in the meta-analysis of changes in LIC. For DFO vs combination therapy (deferiprone and DFO), 43 patients (DFO = 21; combination therapy = 22) were included in the meta–analysis at 6 months and 25 patients (DFO = 14; combination therapy = 11), all from one trial, were included in the quantitative analysis at 12 months	Mortality and morbidity only measured in the one study comparing DFO with placebo. No significant differences reported between the different chelators in terms of reducing iron overload or adverse events [for DFO vs deferiprone, serum ferritin OR = 0.27 (–0.55 to 0.01), LIC ratio of geometric mean = 0.70 (0.53–0.93), adverse events OR = 0.45 (0.24–0.84); for DFO vs combination therapy, serum ferritin OR = 0.72 (–0.07 to 1.50) at 12 months and OR = 1.19 (–0.22 to 2.60) at 6 months]. Thus, no reason was found to change current treatment recommendations
VanOrden 2006[7]	To review the available literature on the pharmacology, pharmacokinetics, efficacy, toxicology, adverse effects, drug interactions and dosage guidelines for deferasirox, an oral iron chelator, in phase III trials	Mean iron excretion, toxicity in animals, absorption rate, distribution, metabolism, elimination, urinary iron excretion, LIC, serum ferritin and adverse events	Data on efficacy, toxicology, adverse effects and pharmacokinetics for deferasirox were obtained from randomised, open-label, blinded clinical trials. Other information was obtained from the manufacturer, including unpublished studies in abstract form as well as available data on deferasirox In terms of efficacy there were two phase I RCTs, three phase II trials (only one of which was a RCT) and one phase III RCT. In terms of adverse events there appeared to be an additional phase II trial (non-RCT). All papers were published between 2003 and 2005	All patients had iron overload requiring chelation therapy. Most patients included in the efficacy studies had thalassaemia (n = 790) but a minority of patients also had MDS (n = 94) and other anaemias including SCD (n = 52)	Deferasirox is as safe and as effective as DFO at daily dosages of 20–30 mg/kg for most patients with thalassaemia (no data exists on subpopulations such as pregnant women and people with renal insufficiency). Adverse events are relatively mild and transient and are likely to include nausea, abdominal pain, diarrhoea and skin rash. Further studies are needed to confirm its efficacy in other chronic transfusion-requiring diseases such as SCD and MDS

Study	Objective and patient population	Outcomes measured	Studies included	Patients included	Findings and conclusions
Abetz 2006[63]	To assess the literature for the impact of iron overload and infusion iron chelation therapy (ICT) on patients' quality of life (QoL), and the availability of QoL instruments for patients undergoing infusion ICT	QoL utilising QoL instruments that have been previously validated elsewhere	15 studies used validated QoL instruments. All papers were published between 1986 and 2004	Patients had thalassaemia (four studies), SCD (six studies) and MDS (four studies)	All of the evaluated studies focused on the impact of thalassaemia, SCD or MDS on patient QoL rather than the impact of ICT on patient QoL. A recurrent theme regarding what might improve patient QoL was the development of an oral drug. Further research is warranted to continue the qualitative and quantitative study of QoL using validated instruments in patients receiving ICT as currently no iron overload-specific QoL instruments exist
Roberts 2007[64]	To determine the effectiveness and safety of deferiprone in people with transfusion-dependent thalassaemia	Mortality (primary outcome) and morbidity (reduced end-organ damage), measures of iron overload including changes in serum ferritin and LIC, adverse events, adherence with DFO and cost of treatment	Overall, ten trials (including two crossover trials) were included examining deferiprone vs DFO, combination therapy (deferiprone and DFO) vs DFO, combination therapy vs deferiprone, and different deferiprone schedules – excluding the last comparison there were nine trials (including one crossover trial). All studies were published between 1990 and 2006	All patients had transfusion-dependent thalassaemia and 398 people from ten trials were included in the full review. For deferiprone vs DFO, 31 patients (deferiprone = 17; DFO = 14) were included in the meta-analysis at 6 months and 104 patients (deferiprone = 100; DFO = 104) at 12 months. No other quantitative analyses were carried out	Mortality and morbidity were not measured in any of the studies. No significant differences reported between the different chelators in terms of reducing iron overload and adverse events were reported in all groups. Thus, no reason was found to change current treatment recommendations

HIC, hepatic iron concentration; IPD, individual patient data; LIC, liver iron concentration; UIE, urinary iron excretion

Appendix 4

Search strategy – clinical and economic evidence

Search strategy and search results

Database	Years	Search strategy	References identified
MEDLINE	1950 to March Week 3 2007	See below	260
EMBASE	1980 to 2007 Week 13	See below	523
ISI Web of Knowledge/Web of Science/Science Citation Index	1945–2007	((deferasirox or exjade or ICL670) and (deferoxamine or DFO or desferal or desferrioxamine)) OR ((deferasirox or exjade or ICL670) and (deferiprone or ferriprox)) OR ((deferoxamine or DFO or desferal or desferrioxamine) and (deferiprone or ferriprox)) OR (deferasirox or exjade or ICL670)	348
ISI Web of Knowledge/ISI Proceedings	1990–2007	As above	76
PubMed (30 March 2007)[a]	2007	(deferasirox OR exjade OR ICL670 OR deferoxamine OR DFO OR desferal OR desferrioxamine OR deferiprone OR ferriprox)	63
The Cochrane Library 2007 (1)[b]	2007 (1)	As above	183 (CENTRAL: 167, Cochrane Database of Systematic Reviews: 8, DARE: 2, HTA: 3, NHS EED: 3)
Total references identified			1453
Duplicates			569
Total			884

a Published in the last 90 days.
b Includes the Cochrane Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment (HTA) database and the NHS Economic Evaluation Database (NHS EED).

Search strategy: Ovid MEDLINE 1950 to March Week 3 2007

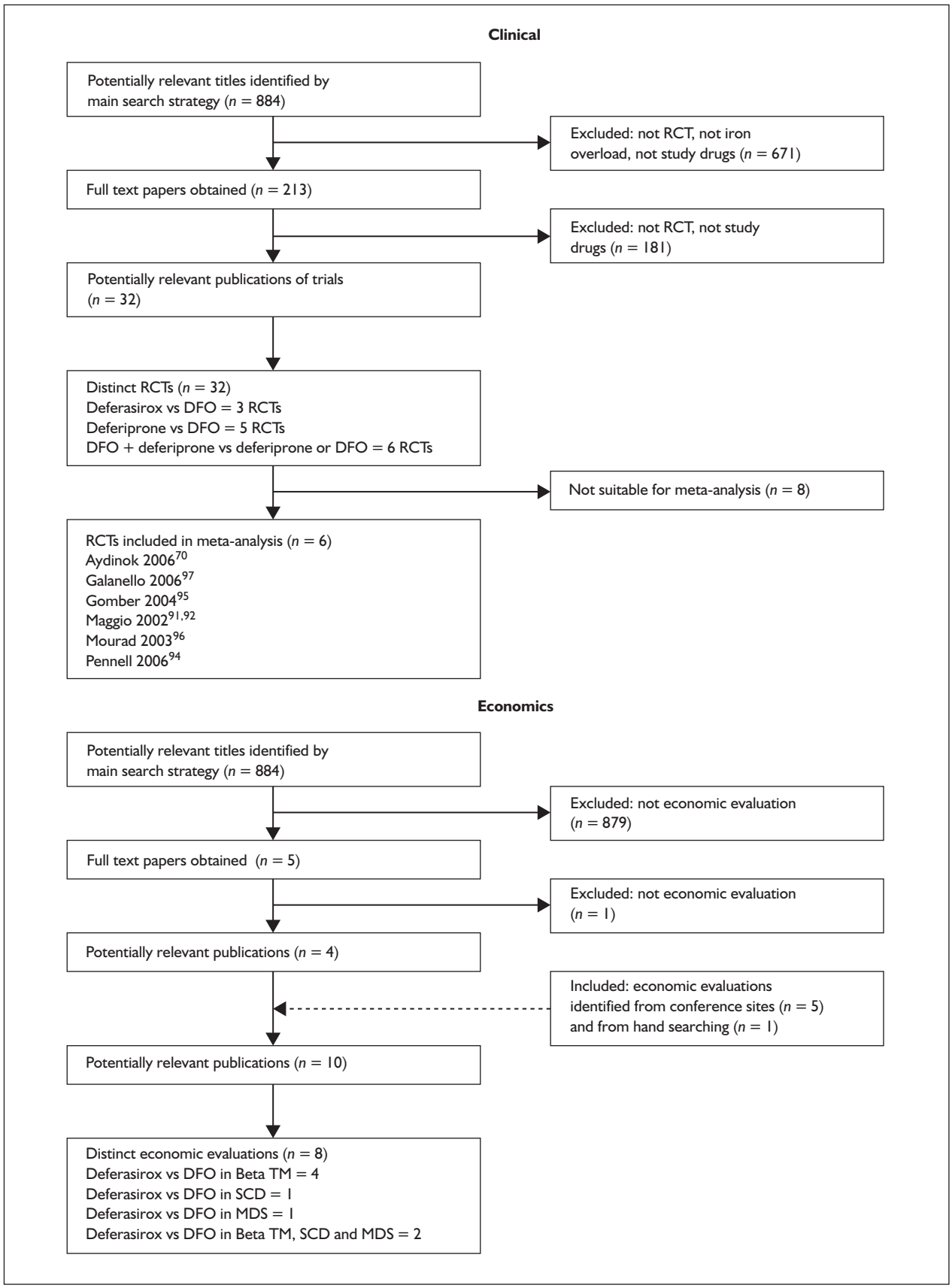
1. (deferasirox or exjade or ICL670).af.
2. (deferoxamine or DFO or desferal or desferrioxamine).af
3. (deferiprone or ferriprox).af.
4. 1 and 2
5. 1 and 3
6. 2 and 3
7. or/4–6
8. 1 or 7
9. exp Iron Chelating Agents/ or exp Chelating Agents/
10. exp beta-Thalassemia/ or exp alpha-Thalassemia/ or exp Thalassemia/
11. exp Anemia/ or Anemia, Sickle Cell
12. exp Myelodysplastic Syndromes/
13. exp Iron Overload/
14. (iron chelat$ or thalassemia$ or anaemia or anemia or myelodysplastic syndrome$ or sickle cell or iron overload$).tw.
15. or/9–14
16. 8 and 15
17. animal/ not (animal/ and human/)
18. 16 and 17

Search strategy: Ovid EMBASE 1980 to 2007 Week 13

1. (deferasirox or exjade or ICL670).af.
2. (deferoxamine or DFO or desferal or desferrioxamine).af
3. (deferiprone or ferriprox).af.
4. 1 and 2
5. 1 and 3
6. 2 and 3
7. or/4–6
8. 1 or 7
9. exp Iron Chelating Agent/ or exp Chelating Agent/
10. exp THALASSEMIA MINOR/ or exp BETA THALASSEMIA/ or exp THALASSEMIA MAJOR/ or exp ALPHA THALASSEMIA/ or exp THALASSEMIA/
11. exp ANEMIA/ or exp SICKLE CELL ANEMIA/
12. exp Myelodysplastic Syndrome/
13. exp Iron Overload/
14. (iron chelat$ or thalassemia$ or anaemia or anemia or myelodysplastic syndrome$ or sickle cell or iron overload$).tw.
15. or/9–14
16. 8 and 15
17. limit 16 to human

Appendix 5

Flow diagram of included studies


Clinical
Potentially relevant titles identified by main search strategy (n = 884)
Excluded: not RCT, not iron overload, not study drugs (n = 671)
Full text papers obtained (n = 213)
Excluded: not RCT, not study drugs (n = 181)
Potentially relevant publications of trials (n = 32)
Distinct RCTs (n = 32)
Deferasirox vs DFO = 3 RCTs
Deferiprone vs DFO = 5 RCTs
DFO + deferiprone vs deferiprone or DFO = 6 RCTs
Not suitable for meta-analysis (n = 8)
RCTs included in meta-analysis (n = 6)
Aydinok 2006[70]
Galanello 2006[97]
Gomber 2004[95]
Maggio 2002[91,92]
Mourad 2003[96]
Pennell 2006[94]
Economics
Potentially relevant titles identified by main search strategy (n = 884)
Excluded: not economic evaluation (n = 879)
Full text papers obtained (n = 5)
Excluded: not economic evaluation (n = 1)
Potentially relevant publications (n = 4)
Included: economic evaluations identified from conference sites (n = 5) and from hand searching (n = 1)
Potentially relevant publications (n = 10)
Distinct economic evaluations (n = 8)
Deferasirox vs DFO in Beta TM = 4
Deferasirox vs DFO in SCD = 1
Deferasirox vs DFO in MDS = 1
Deferasirox vs DFO in Beta TM, SCD and MDS = 2

Appendix 6

Longer-term adverse event information

Search strategy

Ovid MEDLINE 1996 to 2007 Week 30

1. (deferasirox or exjade or ICL670).af.
2. (ae or si or to or co).fs.
3. (safe or safety).ti,ab.
4. side effect$.ti,ab.
5. ((adverse or undesirable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.
6. exp Drug Toxicity/
7. exp adverse drug reaction reporting systems/
8. or/2–7
9. 1 and 8

Ovid EMBASE 1996 to 2007 Week 30

1. (deferasirox or exjade or ICL670).af.
2. (ae or si or to or co).fs.
3. (safe or safety).ti,ab.
4. side effect$.ti,ab.
5. ((adverse or undesirable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.
6. exp adverse drug reaction/
7. exp drug toxicity/
8. exp intoxication/
9. exp drug safety/
10. exp drug monitoring/
11. or/2–10
12. 1 and 11

Selection of evidence

	Number of records
Main search strategy	188
Total references screened	188
Total references included	3

Appendix 7

DFO administration costs

Estimated administration costs associated with DFO assuming 100% balloon infuser usage and 0% balloon infuser usage. Unit costs and other cost items and resource use are based on the results of a costing study undertaken by Novartis (Karen Jewitt, Novartis, July 2007, personal communication).

100% balloon infuser usage

	Unit cost (£)	Patients (%)	No. per patient receiving item	Annual costs per patient (£)
Pump	766.59	0	–	–
Balloon infuser	34.00	100	251.8	8561.20
Portacath	257.94	5	0.5	6.45
Needles for portacath	4.10	5	300	61.50
Portacath surgery	1007.88	5	0.5	25.20
Syringes	0.12	100	55.4	6.65
Needles	0.05	100	300	15.00
Infusion sets	1.16	100	171.2	198.59
Tape	0.66	100	10	6.60
Alcohol pads	0.04	100	310.9	12.44
Gauze	0.03	100	300	9.00
Sharp bins	1.33	100	2	2.66
Battery	2.60	0	–	–
Home delivery costs	274.00	100	1	274.00
DFO administration	100% balloon infuser usage			9179

0% balloon infuser usage

	Unit cost (£)	Patients (%)	No. per patient receiving item	Annual costs per patient (£)
Pump	766.59	100	1	766.59
Balloon infuser	34.00	0	–	–
Portacath	257.94	5	0.5	6.45
Needles for portacath	4.10	5	300	61.50
Portacath surgery	1007.88	5	0.5	25.20
Syringes	0.12	100	55.4	6.65
Needles	0.05	100	300	15.00
Infusion sets	1.16	100	171.2	198.59
Tape	0.66	100	10	6.60
Alcohol pads	0.04	100	310.9	12.44
Gauze	0.03	100	300	9.00
Sharp bins	1.33	100	2	2.66
Battery	2.60	100	2.91	7.57
Home delivery costs	274.00	100	1	274.00
DFO administration	0% balloon infuser usage			1392

Appendix 8

Proportion of SCD and beta-TM patients using a log-normal model

Beta-TM; Cappellini 2006[62]				SCD; Vichinsky 2007[81]			
Age (years)	**Proportions (%)**	**Years**	**Density (%)**	**Age (years)**	**Proportions (%)**	**Years**	**Density (%)**
2–5	9.9	4	2.48	2–5	3.6	4	0.90
6–11	23.0	6	3.83	6–11	23.1	6	3.85
12–15	18.1	4	4.53	12–15	23.6	4	5.90
16–49	48.8	34	1.44	16–49	48.2	34	1.42
50–64	0.2	15	0.01	50–64	1.5	15	0.10
Total	*100*			*Total*	*100*		
Model totals	93			Model totals	97		
Model parameters	Mu	2.8791		Model parameters	Mu	2.8828	
	Sigma	0.8666			Sigma	0.7071	
Sum of squares		0.270%		Sum of squares		0.500%	

DOI: 10.3310/hta13010

Beta-TM; Cappellini 2006[62]					SCD; Vichinsky 2007[81]				
Age (years)	Density (%)	Log-normal model cumulative (%)	Log-normal model density function (%)	SS difference (%)	Age (years)	Density (%)	Log-normal model cumulative (%)	Log-normal model density function (%)	SS difference (%)
2	2.5	2.0	2.0	0.002	2	0.90	0.581	0.581	0.001
3	2.5	4.2	2.3	0.001	3	0.90	1.715	1.134	0.001
4	2.5	7.1	2.9	0.002	4	0.90	3.585	1.871	0.009
5	2.5	10.5	3.3	0.007	5	0.90	6.140	2.555	0.027
6	3.8	14.1	3.6	0.001	6	3.85	9.257	3.117	0.005
7	3.8	17.8	3.7	0.000	7	3.85	12.793	3.536	0.001
8	3.8	21.6	3.8	0.000	8	3.85	16.611	3.818	0.000
9	3.8	25.3	3.7	0.000	9	3.85	20.593	3.982	0.000
10	3.8	28.9	3.6	0.000	10	3.85	24.641	4.048	0.000
11	3.8	32.5	3.5	0.001	11	3.85	28.680	4.039	0.000
12	4.5	35.8	3.4	0.013	12	5.90	32.652	3.972	0.037
13	4.5	39.1	3.2	0.016	13	5.90	36.514	3.863	0.042
14	4.5	42.2	3.1	0.021	14	5.90	40.239	3.725	0.047
15	4.5	45.1	2.9	0.025	15	5.90	43.806	3.567	0.054
16	1.4	47.9	2.8	0.018	16	1.42	47.204	3.398	0.039
17	1.4	50.5	2.6	0.014	17	1.42	50.426	3.223	0.033
18	1.4	53.0	2.5	0.011	18	1.42	53.473	3.046	0.027
19	1.4	55.4	2.3	0.008	19	1.42	56.344	2.871	0.021
20	1.4	57.6	2.2	0.006	20	1.42	59.045	2.701	0.016
21	1.4	59.7	2.1	0.004	21	1.42	61.581	2.536	0.013
22	1.4	61.6	2.0	0.003	22	1.42	63.959	2.378	0.009
23	1.4	63.5	1.9	0.002	23	1.42	66.186	2.227	0.007
24	1.4	65.2	1.8	0.001	24	1.42	68.271	2.085	0.004
25	1.4	66.9	1.7	0.000	25	1.42	70.220	1.950	0.003
26	1.4	68.5	1.6	0.000	26	1.42	72.043	1.823	0.002

continued

Beta-TM; Cappellini 2006[62]					SCD; Vichinsky 2007[81]				
Age (years)	Density (%)	Log-normal model cumulative (%)	Log-normal model density function (%)	SS difference (%)	Age (years)	Density (%)	Log-normal model cumulative (%)	Log-normal model density function (%)	SS difference (%)
27	1.4	69.9	1.5	0.000	27	1.42	73.747	1.704	0.001
28	1.4	71.3	1.4	0.000	28	1.42	75.339	1.592	0.000
29	1.4	72.7	1.3	0.000	29	1.42	76.826	1.487	0.000
30	1.4	73.9	1.2	0.000	30	1.42	78.216	1.390	0.000
31	1.4	75.1	1.2	0.001	31	1.42	79.514	1.299	0.000
32	1.4	76.2	1.1	0.001	32	1.42	80.728	1.214	0.000
33	1.4	77.2	1.1	0.001	33	1.42	81.863	1.134	0.001
34	1.4	78.2	1.0	0.002	34	1.42	82.923	1.061	0.001
35	1.4	79.2	0.9	0.002	35	1.42	83.915	0.992	0.002
36	1.4	80.1	0.9	0.003	36	1.42	84.843	0.928	0.002
37	1.4	80.9	0.8	0.003	37	1.42	85.711	0.868	0.003
38	1.4	81.7	0.8	0.004	38	1.42	86.524	0.813	0.004
39	1.4	82.5	0.8	0.005	39	1.42	87.285	0.761	0.004
40	1.4	83.2	0.7	0.005	40	1.42	87.998	0.713	0.005
41	1.4	83.9	0.7	0.006	41	1.42	88.666	0.668	0.006
42	1.4	84.6	0.7	0.006	42	1.42	89.293	0.626	0.006
43	1.4	85.2	0.6	0.007	43	1.42	89.880	0.588	0.007
44	1.4	85.8	0.6	0.007	44	1.42	90.432	0.551	0.008
45	1.4	86.3	0.6	0.008	45	1.42	90.949	0.517	0.008
46	1.4	86.9	0.5	0.008	46	1.42	91.435	0.486	0.009
47	1.4	87.4	0.5	0.009	47	1.42	91.892	0.457	0.009
48	1.4	87.9	0.5	0.009	48	1.42	92.321	0.429	0.010

Beta-TM; Cappellini 2006[62]					SCD; Vichinsky 2007[81]				
Age (years)	**Density (%)**	**Log-normal model cumulative (%)**	**Log-normal model density function (%)**	**SS difference (%)**	**Age (years)**	**Density (%)**	**Log-normal model cumulative (%)**	**Log-normal model density function (%)**	**SS difference (%)**
49	1.4	88.3	0.5	0.009	49	1.42	92.724	0.403	0.010
50	0.0	88.8	0.4	0.002	50	0.10	93.104	0.380	0.001
51	0.0	89.2	0.4	0.002	51	0.10	93.461	0.357	0.001
52	0.0	89.6	0.4	0.002	52	0.10	93.797	0.336	0.001
53	0.0	90.0	0.4	0.001	53	0.10	94.114	0.317	0.000
54	0.0	90.4	0.4	0.001	54	0.10	94.412	0.298	0.000
55	0.0	90.7	0.4	0.001	55	0.10	94.693	0.281	0.000
56	0.0	91.0	0.3	0.001	56	0.10	94.959	0.265	0.000
57	0.0	91.4	0.3	0.001	57	0.10	95.209	0.250	0.000
58	0.0	91.7	0.3	0.001	58	0.10	95.445	0.236	0.000
59	0.0	92.0	0.3	0.001	59	0.10	95.668	0.223	0.000
60	0.0	92.2	0.3	0.001	60	0.10	95.879	0.211	0.000
61	0.0	92.5	0.3	0.001	61	0.10	96.078	0.199	0.000
62	0.0	92.8	0.3	0.001	62	0.10	96.266	0.188	0.000
63	0.0	93.0	0.2	0.001	63	0.10	96.444	0.178	0.000
64	0.0	93.3	0.2	0.000	64	0.10	96.612	0.168	0.000

SS, sum of squares.

Appendix 9

Budget impact estimates for new cases of iron overload

The following tables show the budget impact assessments for new cases of iron overload in beta-TM and SCD patients. These estimates are based on the assumption that the 15 new cases of iron overload in beta-TM patients occur at the age of 2 years, whereas the 16 new cases of iron overload in SCD patients occur at the age of 4 years.

Budget impact for beta-TM patients

Age	Budget impact deferasirox	Budget impact DFO pump	Budget impact DFO infuser	Budget impact deferiprone	Deferasirox vs DFO pump	Deferasirox vs DFO infuser	Deferasirox vs deferiprone
2	£65,795	£40,881	£157,687	£32,905	£24,914	–£91,891	£32,890

Budget impact for SCD patients

Age	Budget impact deferasirox	Budget impact DFO pump	Budget impact DFO infuser	Budget impact deferiprone	Deferasirox vs DFO pump	Deferasirox vs DFO infuser	Deferasirox vs deferiprone
4	£67,645	£41,814	£132,855	£32,017	£25,831	–£65,209	£35,629

Appendix 10

Prescribing pattern of chelators

This table shows the proportion of patients receiving each chelator according to age (Bernadette Modell, 2007, personal communication). The data is from 1999, hence prescribing patterns may have changed since then, with more patients (and at an earlier age) receiving deferiprone and DFO via the balloon infuser.

Age (years)	DFO pump (%)	DFO infuser (%)	Deferiprone (%)
2	100	0	0
3	100	0	0
4	100	0	0
5	100	0	0
6	100	0	0
7	100	0	0
8	100	0	0
9	100	0	0
10	90	10	0
11	80	20	0
12	70	30	0
13	60	40	0
14	60	40	0
15	60	40	0
16	60	40	0
17	60	40	0
18+	40	40	20

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The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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ISSN 1366-5278