National Institute for Health and Clinical Excellence

MultipleTechnology Appraisal (MTA)

Desferrioxamine, deferiprone and deferasirox for the treatment of chronic iron overload in people with thalassaemia

Response to consultee and commentator comments on the draft scope

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Commissioning Support Appraisals Service (CSAS)	None.	Comment noted.
	Royal College of Paediatrics and Child Health	The College thinks this is correct, but it fails to mention other groups who may need regular transfusions and thus benefit from modern iron chelation, e.g. congenital anaemias, sickle cell disease. The prevalence information appears to be the gene frequency in different ethnic populations (what we interpret from the term, 'carry thalassaemia'). We think it should indicate the prevalence of those affected by the condition.	An appraisal of treatment for chronic iron overload for conditions other than thalassaemia has not been referred to NICE by the Department of Health. The scope has been amended to make it clear that the data relates to those who carry the gene, rather than those who have thalassaemia.

Section	Consultees	Comments	Action
	Royal College of Pathologists and British Society of Haematology	The classification of thalassaemia is not quite right. Alpha thalassaemia major is not seen in the UK because affected infants die before birth (unlike beta thalassaemia major). However a significant number of patients have a syndrome intermediate between thalassaemia major and thalassaemia minor. This is called Thalassaemia Intermedia and this should be included as it is a disorder associated with significant iron overload due to either increased oral iron absorption or intermittent blood transfusions. Some patients with TI do require regular transfusions but in general less then 7 episodes per year.	The background section of the scope has been amended accordingly.
	ApoPharma Inc	The background section is correct although it appears that the prevalence noted in the last sentence of the second paragraph may relate to those who carry the gene, rather than those who have thalassaemia. If so, it should read 'It is estimated that around 3-10% of people of Indian origin, 4.5% of Pakistani origin, 8% of Bangladeshi origin, 17% of Cypriotic origin, 0.5-1% of Afro-Caribbean origin and 0.1% of White people carry a thalassaemia gene.'	The scope has been amended to make it clear that the data relates to those who carry the gene, rather than those who have thalassaemia.
	Medicines and Healthcare products Regulatory Agency	The second sentence in the first paragraph states: As there are no natural means of removing excess iron, iron gradually accumulates. In fact, there are limited means by which iron is lost; these include menstruation and sloughing intestinal mucosal cells. Consider saying: 'The body has very limited capacity for removing iron' The second sentence in para 3 under 'Background' states: The risk of iron overload increases once patients have received approximately 20 transfusions. The number of units per transfusion can vary and it might be better to state the number of units rather than '20 transfusions'?	The scope has been amended accordingly.
	Eastern and Coastal Kent NHS	None.	Comment noted.

Section	Consultees	Comments	Action
	NHS Northamptonshire	Satisfactory	Comment noted.
	NHS Sickle Cell and thalassaemia Screening Programme	Satisfactory	Comment noted.
	Novartis Pharmaceuticals UK	Add 'Chronic iron overload therefore leads to early morbidity and mortality' to the first paragraph of the background section.	The morbidity and mortality associated with chronic iron overload is included in the background section.
	UK Forum on Haemoglobin Disorders	I am concerned about some of the terminology used. For carrier states, more usual description is 'carriers of beta thalassaemia' rather than 'beta thalassaemia minor' – the latter has not been regularly used for some time. We usually try to keep to agreed terms to avoid confusion, mostly based on those included in Accessible Publishing of Genetic Information APoGI – found at www.chime.ucl.ac/APoGI. I would probably omit reference to alpha thalassaemia, alpha thalassaemia major usually results in intrauterine death, if not detected early, and is in practice not a clinical entity, and alpha thalassaemia carrier state irrelevant here. Transfusions in beta thalassaemia major are usually given in the UK at 4 weekly, thus ~12 transfusions a year rather than the suggested 8. In terms of ethnicity, 'Caucasians' would be clearly preferable to 'white people'. African-Caribbean now more usual descriptor, rather than Afro-Caribbean. In indicating that 3-4 units of blood per month are required, it should state that this is for adult patients, obviously starting volumes in children are smaller. Risk of iron overload usually reckoned to be after 10 transfusions, rather than 20, so coming up to a year on transfusions. There is no mention of patients with sickle cell disease on regular	The background section of the scope has been amended to take into account the comments received during consultation This topic has been referred to NICE by the Department of Health as a Multiple Technology Appraisal of desferrioxamine, deferiprone and deferasirox for the treatment of chronic iron overload in people with thalassaemia. Consequently,

Section	Consultees	Comments	Action
		transfusions, increasingly common now to treat / prevent stroke particularly, requiring iron chelation – this is a significant omission. Desferal –[incidentally mis-spelt towards end of the paragraph describing its use] is never now used intramuscularly – too short acting to be of as much value, prolonged infusions are required. This has been the case for 25 – 30 years now, it was initially used i.m when first introduced mid 70's. In Deferasirox paragraph, it suggests that 7 ml/kg/month requires 2 or more transfusions per month, this is not true, this and higher volumes per month can be transfused at one time.	all other indications are beyond the remit of this appraisal. The scope has been amended to reflect the wording used in the summaries of product characteristics. This is taken from the summary of product characteristics for deferasirox.
	United Kingdom Thalassaemia Society	In the definition of "White people" does it perhaps refer to an Anglo Saxon population? Other population groups such as Greek, Italian, Arab and Far Eastern have been omitted.	The wording for this section has been amended following the consultation.
The technology/ intervention	Commissioning Support Appraisals Service (CSAS)	Where data concerning different devices for administering desferrioxamine infusion is available this could be considered. Likewise the patient preference for home or hospital based infusions could be considered.	Comment noted.

Section	Consultees	Comments	Action
	Royal College of Paediatrics and Child Health	Yes.	Comment noted.
	Royal College of Pathologists and British Society of Haematology	The three drugs are listed but there are currently at least 4 different chelation regimes used: desferrioxamine single agent (both IV and sc), deferasirox single oral agent, deferiprone single oral agent, and various combinations of therapy that include deferasirox and deferiprone. There are also clinical trials with combinations of deferasirox and desferrioxamine underway as well as deferasirox and deferiprone. The MTA seems rather restricted.	The 'Other considerations' section of the scope states that where the evidence allows, combinations of the different iron chelators will be considered.
	ApoPharma Inc	The description of the technologies is accurate	Comment noted.

Section	Consultees	Comments	Action
	Medicines and Healthcare products Regulatory Agency	The last three lines under 'Desferrioxamine' state: haemolytic anaemia and other chronic anaemia's. Defesral is administered parenterally and desferrioxamine mesilate (Hospira) is administered intramuscularly, intravenously, or subcutaneously. Please remove the extraneous apostrophe from anaemia's and change Defesral to Desferal.	The scope has been amended accordingly.
		The wording implies that the mode of administration of the two products may be different. In fact both products can be given intravenously, subcutaneously or by intramuscular injection.	The technology description aims to be as close as possible to the summary of product characteristics (SPC) for each technology. The mode of administration has therefore been taken verbatim from the SPCs.
		The Proposed International Nonproprietary Name for desferrioxamine mesilate is 'Deferoxamine Mesilate' (the US Adopted Name, USAN, is 'Deferoxamine Mesylate')	Comment noted
		Under Deferasirox, it may be worth clarifying that the product is supplied as dispersible tablets. The current wording might imply that the product is supplied as a suspension. Before administration, the tablets are dispersed in water, orange juice or apple juice to form a fine suspension.	The scope has been amended accordingly.
	Eastern and Coastal Kent NHS	Where data concerning different devices for administering desferrioxamine infusion is available this could be considered. Likewise the patient preference for home or hospital based infusions could be considered.	The different devices used is outside of the remit for this appraisal.
	NHS Northamptonshire	Satisfactory	Comment noted.

Section	Consultees	Comments	Action
	NHS Sickle Cell and thalassaemia Screening Programme	Satisfactory	Comment noted.
	Novartis Pharmaceuticals UK	The description of technologies is accurate but see suggested paragraph below for desferrioxamine: Desferrioxamine mesilate (Desferal, Novartis; Desferrioxamine mesilate, Hospira) has a UK marketing authorisation for the treatment of chronic iron overload, including acute iron poisoning; primary and secondary haemochromatosis including thalassaemia and transfusional haemosiderosis in patients receiving regular transfusions; in patients in whom concomitant disorders (for example, severe anaemia, hypoproteinaemia, renal or cardiac failure) preclude phlebotomy; and for the diagnosis of iron storage disease and certain anaemias. Desferal/DFO is administered parenterally.	The technology description aims to be as close as possible to the summary of product characteristics (SPC) for each technology. The mode of administration has therefore been taken verbatim from the SPCs.
	UK Forum on Haemoglobin Disorders	As above.	Comment noted.

Section	Consultees	Comments	Action
	United Kingdom Thalassaemia Society	Yes. The information should reflect the fact that we do not believe there should be a restriction on the basis of marketing authorisation as discussed in our response to the questions for consultation - Appendix A.	Following comments received from consultations on earlier versions of the draft scope, the remit received by NICE from the Department of Health is 'To appraise the clinical and cost effectiveness of desferrioxamine, deferiprone and deferasirox for the treatment of chronic iron overload in people with thalassaemia.' In addition, the 'Other considerations' section of the scope states that where the evidence allows, combinations of the different iron chelators will be considered.
Population	Commissioning Support Appraisals Service (CSAS)	None	Comment noted.

Section	Consultees	Comments	Action
	Royal College of Paediatrics and Child Health	We think this should at least mention other groups needing regular transfusions; iron chelation principles are as likely to apply to them as not. Failure to do so will possibly result in refusal of funding for appropriate treatment for such, rarer, cases. We think it could be helpful to consider iron overload cardiomyopathy separately: (i) Atrical Ejection Force and MRI (especially T2* multislice multi-echo MRI) are useful for early detection of myocardial iron overload (ii) Gene therapy, hepcidin (HAMP) and calcium channel blockers are now being investigated for treating iron overload cardiomyopathy.	An appraisal of treatment for chronic iron overload for conditions other than thalassaemia has not been referred to NICE by the Department of Health.
	Royal College of Pathologists and British Society of Haematology	1) Thalassaemia Intermedia should be included as these are patients who develop toxicity from iron overload. These patients by virtue of the anaemia cannot be venesected to remove excess iron. They can die as a consequence of the iron loading. A randomised study for this indication has been undertaken to assess the efficacy and safety of chelation with Deferasirox in this group of patients. Currently these patients will receive desferrioxamine or deferiprone or a combination of these when the iron burden becomes too high. 2) Sickle cell anaemia is about 10 times more common than thalassaemia major in the UK. About10-20% of patients with sickle cell syndromes require chronic blood transfusion and hence require chelation therapy. Even though deferasirox is the only oral treatment licensed for this indication, it may prove difficult, time consuming and unpredictable to obtain finding for treatment with the anticipated future re-organisation of primary care and without specific guidance from NICE about the benefits of chelation therapy. 3) Rare anaemia's should be included. These include Diamond Blackfen, Sideroblastic anaemia, Congenital dyserythropoeitic anaemias, transfusion dependant PK and G6PD and chronic haemolytic anaemias. These are all by definition rare, affect young patients with otherwise good life expectancy (if appropriately treated) and all develop similar problems related to iron	Thalassaemia Intermedia has been added to the scope. An appraisal of treatment for chronic iron overload for conditions other than thalassaemia has not been referred to NICE by the Department of Health.

Section	Consultees	Comments	Action
		overload due to blood transfusions. Prospective studies have been undertaken to assess the efficacy and safety of deferasirox in these patients. Many of these patients either already receive Deferasirox or are on desferrioxamine infusions. 4) There is no consideration of age in the way the population is defined. However the licensing of chelation is age specific. For example deferiprone is not licensed for children under 6 as there are 'No data under 6 and limited under 10 ' Whereas there is no age restriction for deferasirox or deferoxamine use by age.	Comments noted. The scope document provides only a brief description of the technology. These details will be taken into account by the Appraisal Committee at the time of issuing guidance. The 'Other considerations' section of the scope states that where appropriate, treatment of children and adults will be considered separately. .
	ApoPharma Inc	Thalassaemia is the correct population, as opposed to any transfusional anaemia, because there are sufficient data on which to draw conclusions on health outcomes. However, the designation of "thalassaemia major" may be restrictive and its designation may not necessarily have been documented in all cases. The key element to address is that a patient has thalassaemia and the patient has become iron overloaded, primarily as a result of blood transfusions. Thus, we would propose that the wording for the specified population be slightly modified to "People with thalassaemia who have developed chronic iron overload following blood transfusions"	The scope has been amended accordingly.

Section	Consultees	Comments	Action
	Medicines and Healthcare products Regulatory Agency	In addition to people with thalassaemia, iron chelation is also required by people with myelodysplastic syndrome and sickle cell disease, but not all iron chelators are licensed for managing iron overload in these conditions.	An appraisal of treatment for chronic iron overload for conditions other than thalassaemia has not been referred to NICE by the Department of Health.
	Eastern and Coastal Kent NHS	None.	Comment noted.
	NHS Northamptonshire	Satisfactory	Comment noted.
	NHS Sickle Cell and thalassaemia Screening Programme	Now restricted to beta thalassaemia major. We had previously discussed inclusion of other conditions, particularly sickle cell disease, where about 10-20% of patients require regular transfusions, and this is probably a larger group of transfusion-requiring patients in England than thalassaemia major.	An appraisal of treatment for chronic iron overload for conditions other than thalassaemia has not been referred to NICE by the Department of Health.
	Novartis Pharmaceuticals UK	We agree that the population has been defined appropriately. Children 2 to 5 years should be considered separately as they represent a group with special needs due to the problems with administering desferrioxamine Patients with significant cardiac iron overload (indicated by a T2* of less than 6 milliseconds) where deferiprone and DFO are used in combination should be considered separately as this a group with very high mortality rates due to cardiac complications.	The 'Other considerations' section of the scope now states that, where appropriate, treatment of children and adults will be considered separately and where the evidence allows, patients with significant cardiac iron overload will be considered as a subgroup.

Section	Consultees	Comments	Action
	UK Forum on Haemoglobin Disorders	As above, suggest omit alpha thalassaemia, and include sickle cell disease and other transfusion dependent anaemias [Blackfan Diamond etc] – tho numbers of latter are small. Sickle cell numbers large and growing – will come to dominate the clinical population requiring iron chelation. Assessments of efficacy for patients with established significant heart iron will need to be made separately from those with low heart iron and significant liver iron. Guidance will also be needed for those with low total iron, where treatment is to avoid iron accumulation from ongoing transfusions, rather than to treat it.	The background section of the scope has been amended with regard to alpha thalassaemia. An appraisal of treatment for chronic iron overload for conditions other than thalassaemia has not been referred to NICE by the Department of Health. The scope now states that, where the evidence allows, patients with significant cardiac iron overload will be considered as a subgroup
	United Kingdom Thalassaemia Society	Please see our response in Answers to questions for consultation - Appendix A.	Comment noted.
Comparators	Commissioning Support Appraisals Service (CSAS)	Combination therapies could be considered.	The 'Other considerations' section of the scope states that where the evidence allows, combinations of the different iron chelators will be considered.
	Royal College of Paediatrics and Child Health	Appropriate.	Comment noted.
	Royal College of Pathologists and British Society of Haematology	The technologies being appraised are currently all being used for iron chelation within the NHS.	Comment noted.

Section	Consultees	Comments	Action
	ApoPharma Inc	The three iron chelators listed are the only pharmacological agents available for the treatment of chronic iron overload. It should be noted that deferoxamine and deferiprone (Ferriprox) are frequently used in combination in clinical practice; in this combination the two agents are more effective than either agent alone. This provides four potential treatment regimens; deferoxamine monotherapy, deferiprone monotherapy, deferasirox (Exjade) monotherapy and deferoxamine and deferiprone combination therapy.	The 'Other considerations' section of the scope states that where the evidence allows, combinations of the different iron chelators will be considered.
	Medicines and Healthcare products Regulatory Agency	It should be noted that deferiprone is licensed for use in patients in whom desferrioxamine is contraindicated or is inadequate.	This is included in the technology section.
	Eastern and Coastal Kent NHS	Combination therapies could be considered.	The 'Other considerations' section of the scope states that where the evidence allows, combinations of the different iron chelators will be considered.
	NHS Northamptonshire	Satisfactory	Comment noted.
	NHS Sickle Cell and thalassaemia Screening Programme	Need to consider the different ways in which chelation therapy is administered in practice: Desferrioxamine via sub cut infusion using electric syringe driver pump, via disposable elastomeric pumps. Desferrioxamine given via continuous iv infusion via indwelling iv device. Combination chelation therapy: desferrioxamine plus deferiprone- sequential and simultaneous regimes.	The scope document provides only a brief description of the technologies. Method of administration will be considered as part of the appraisal process but a consideration of the different devices used is outside of the remit for this appraisal.

Section	Consultees	Comments	Action
	Novartis Pharmaceuticals UK	We suggest the following wording: “Deferasirox, deferiprone and desferrioxamine will be compared with each other as appropriate in line with their licensed indication.” We would emphasise the following comparators in relation to the technologies: Deferasirox is licensed as a first line treatment option for patients with thalassaemia major who are 6 years or older and receive frequent blood transfusions. The current standard of treatment is DFO and is therefore the relevant comparator. Deferasirox is licensed as a second line therapy for patients aged 2 to 5 years old when DFO is contraindicated or inadequate. • However, DFO remains the comparator for this patient group in clinical practice. For many years there was no other chelator specifically licensed for this patient group and in the absence of any other licensed chelator, DFO was given, even when it was considered to provide suboptimal treatment. A key issue is that DFO is given by subcutaneous infusion over a period of 8 to 12 hours per day, 5 to 7 times per week, which is considered an extremely onerous dosage regime for young children. Clinical opinion suggests that there is an increased likelihood of injection site reactions in this age group which also contributes to the reduced compliance/adherence observed with DFO. Since the availability of deferasirox, 2 to 5 year olds are now treated with deferasirox due to the advantages conferred by its once-daily oral formulation and because it is the only oral drug licensed for this age group.	Deferasirox, deferiprone and desferrioxamine will be compared with each other as appropriate. This has been stated in the ‘comparators’ section of the draft scope. Where the evidence allows, combinations of the different iron chelators will be considered.

Section	Consultees	Comments	Action
		Deferasirox is licensed as a second line therapy for patients with beta thalassaemia major with iron overload due to infrequent blood transfusions when DFO is contraindicated or inadequate • The infrequent blood transfusions (<7ml/kg/month of packed red blood cells) patient group considered for second line deferasirox treatment is an 'artificial' patient sub-population. In clinical practice patients are not differentiated for first or second line treatment with deferasirox solely based on the frequency of blood transfusions. Rather patients are treated with oral deferasirox as a first line treatment option when they are diagnosed with thalassemia major and are being transfused regularly. This therefore means that DFO is the appropriate comparator in this instance because it is the current standard of care that is replaced by deferasirox.	
		Deferiprone is not licensed for the 2 to 5 year age group. The deferiprone SPC states that there are limited data available on the use of deferiprone in children between 6 and 10 years of age, and no data on deferiprone use in children under 6 years of age. Deferiprone is licensed as a second line treatment option when desferrioxamine is contraindicated or inadequate. This is reflected in UK guidelines and clinical practice where deferiprone is recommended as a second line treatment option when both desferrioxamine and deferasirox are contraindicated or inadequate. Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK 2008 pg 35) In fact, in clinical practice, deferiprone is mainly used as combination therapy with desferrioxamine patients with significant cardiac iron overload (T2* < 6 ms), which is reflective of the clinical data that has been obtained using deferiprone in combination with desferrioxamine. Thus it must be emphasised that although both deferasirox and deferiprone are oral chelators, their respective licences, clinical practice and the available evidence base precludes them from a head to head comparison.	

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<tr><th>Section</th><th>Consultees</th><th>Comments</th><th>Action</th></tr>
<tr><td></td><td></td><td>Summary of technologies and the appropriate comparators
<table>
<tr><th>Technology</th><th>Population</th><th>Comparator</th></tr>
<tr><td rowspan="3">Deferasirox</td><td>1st line for β t al patients > 6 years wit frequent bloo tra sfusions</td><td>DFO</td></tr>
<tr><td>2nd line for β- thal patients with inf e quent blood transfusi n</td><td>DFO (see explanation above)</td></tr>
<tr><td>2nd line for 2 to 5 year patients</td><td>DFO (see explanation above)</td></tr>
<tr><td>Deferiprone in combination with DFO</td><td>2nd line for β- thal patients with cardiac iron overload (T2*<6 ms)</td><td>DFO (see explanation bove</td></tr>
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<tr><td></td><td>UK Forum on Haemoglobin Disorders</td><td>Yes these are the 3 currently available agents for use in transfusional iron overload, they are the correct agents to consider and compare.</td><td>Comment noted.</td></tr>
<tr><td></td><td>United Kingdom Thalassaemia Society</td><td>Yes, these are the standard treatment(s) currently used in the NHS with which the technology should be compared.
The clinicians now have the ability and the choice to formulate an optimal chelation management plan tailor made to the patient using one or a combination of chelators. Recent publications describe the standardisation of such innovative practices as alternative care and they should be taken into consideration. (see TIF Magazine, Angastiniotis, M., Working together to remove excess iron, Nov. 2010, p.47).</td><td>The ‘Other considerations’ section of the scope states that where the evidence allows, combinations of the different iron chelators will be considered.</td></tr>
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Section	Consultees	Comments	Action
Outcomes	Commissioning Support Appraisals Service (CSAS)	None.	Comment noted.
	Royal College of Paediatrics and Child Health	We think it will be important to look carefully at the costs vs benefits of the oral therapy vs parenteral therapy. This should include analysis of patient choice between the treatments (via a satisfaction survey).	The economic analysis will take into account all relevant costs and benefits. Utility measures will be incorporated to factor in patient preferences and quality of life with the treatments under consideration.
	Royal College of Pathologists and British Society of Haematology	Outcome measures are broadly appropriate but ferritin is not a reliable or suitable measure of iron balance. Iron balance is measured either in the long term by changes in liver iron concentration or in the short term by formal metabolic balance studies. A further measure of long-term efficacy that should be considered is the effect on liver pathology. This is now overtaking heart disease as the leading cause of death in older patients with thalassaemia major.	Serum ferritin levels has been removed as an outcome measure and replaced with 'effects on iron balance'.
	ApoPharma Inc	The outcomes listed in the draft scope capture the most important health-related outcomes in people with thalassaemia who have developed chronic iron overload following blood transfusions.	Comment noted.
	Medicines and Healthcare products Regulatory Agency	Consider including more patient-oriented outcomes. As noted under Background, iron overload can lead to complications such as cirrhosis, diabetes, growth impairment and sterility.	It is expected that the outcome measures listed in the scope are comprehensive and will incorporate these complications.
	Eastern and Coastal Kent NHS	None.	Comment noted.

Section	Consultees	Comments	Action
	NHS Northamptonshire	Satisfactory	Comment noted.
	NHS Sickle Cell and thalassaemia Screening Programme	The means of measuring liver iron content needs to be defined. (Three methodologies used are: biopsy content by direct chemical analysis-rarely used: T2* MRI and R2 MRI (Ferriscan), and liver iron should be assessed as a means of demonstrating (i) Reduction in liver iron stores in heavily iron loaded patients and (ii) maintenance of stable iron balance in non-heavily loaded patients. Also clinical outcomes related to clinical toxicity of iron need to be specified: (i) prevention and (ii) treatment of complications through chelation of iron affecting specific organ systems, including cardiac hepatic and endocrine disease.	The scope document provides only a brief summary of the background and technology. This level of detail is not required in the scope.
	Novartis Pharmaceuticals UK	We suggest that mortality is excluded as an outcome: •The key deferasirox trials were not designed to measure long term outcomes such as mortality but to show deferasirox as an effective treatment for the control of chronic iron overload in a wide range of patients, and to be as effective and safe as desferrioxamine using appropriate markers of outcome (non-inferiority trial).	Mortality is of interest as an outcome and will be modelled as part of the economic analysis despite not being an explicit part of the trial design.
	UK Forum on Haemoglobin Disorders	Yes but an indication of methodology as to how liver iron, total body iron excretion, cardiac iron content / function are to be assessed.	The scope document provides only a brief summary of the key issues. This level of detail is not required in the scope.
	United Kingdom Thalassaemia Society	They will capture the most important health benefits but the adverse effects of treatment need to be further clarified and expanded. Furthermore, lack of efficacy could potentially be one such AE indirectly.	All relevant adverse effects of treatment will be taken into account. The scope document provides only a brief summary of the key issues. This level of detail is not required in the scope.

Section	Consultees	Comments	Action
Economic analysis	Commissioning Support Appraisals Service (CSAS)	None.	Comment noted.
	Royal College of Paediatrics and Child Health	Satisfactory.	Comment noted.
	Royal College of Pathologists and British Society of Haematology	Time horizon is OK.	Comment noted.
	ApoPharma Inc	No comments.	Comment noted.
	Eastern and Coastal Kent NHS	None.	Comment noted.
	NHS Northamptonshire	Satisfactory	Comment noted.
	NHS Sickle Cell and thalassaemia Screening Programme	Seems reasonable.	Comment noted.

Section	Consultees	Comments	Action
	Novartis Pharmaceuticals UK	•We suggest that a short term analysis is appropriate in this instance because as highlighted earlier, there is limited evidence to distinguish the chelators in terms of their impact on long term outcomes. The key trials and the evidence base in general does not measure and prove differences in long term outcomes. The main difference that can be directly measured and compared is the improvements in quality of life conferred by the chelators. Deferasirox is known to have a significant impact on the quality of life of patients because of its oral properties, compared to desferrioxamine given subcutaneously over a period of 8 to 12 hours per day, 5 to 7 times per week. In addition, deferasirox confers better quality of life compared to deferiprone that has a worse side effect profile, requires weekly monitoring and is dosed three times per day – compared to deferasirox that is dosed once a day. •Consequently, a short term time horizon is considered reasonable and appropriate to demonstrate the cost-effectiveness of deferasirox.	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared. A time horizon shorter than lifetime could be justified if there is no differential mortality effect between options, and the differences in costs and HRQL relate to a relatively short period (for example, in the case of an acute infection). Consideration of the time horizon and the uncertainty around the extrapolation of data beyond the duration of the clinical trials is a critical component of the appraisal.
	UK Forum on Haemoglobin Disorders	As treatment is life long for most patients, the time horizon needs to be in terms of decades.	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.

Section	Consultees	Comments	Action
	United Kingdom Thalassaemia Society	We agree that an economic time horizon as long as possible should be used to capture the macro scale benefits of each chelator. We believe that there will be differences in the incremental cost per quality-adjusted life year, between children, adolescents and adults, mainly due to blood transfusion requirements at these ages and associated dosing. Also we question the process for appraising the additional costs of non or poor compliance that will result in both medical as well as personal and a social problems. What will be the process to capture the ICER per QALY resulting from the financial burden as well as the losses to economic activity of the family with an affected child in these associated cases?	The 'Other considerations' section of the scope states that where appropriate, treatment of children and adults will be considered separately. It also states that, if the evidence allows, the effect of adherence to treatment on outcomes will be considered. As per the NICE Guide to the methods of technology appraisal, financial costs relevant to the NHS/personal social services (PSS) should be used as the basis of costing. Productivity costs and costs borne by patients that are not reimbursed by the NHS and PSS should be excluded.
Equality and Diversity	Commissioning Support Appraisals Service (CSAS)	None.	Comment noted.

Section	Consultees	Comments	Action
	Royal College of Paediatrics and Child Health	By excluding congenital anaemias the appraisal may inadvertently discriminate against the white population.	This topic has been referred to NICE by the Department of Health as a Multiple Technology Appraisal of desferrioxamine, deferiprone and deferasirox for the treatment of chronic iron overload in people with thalassaemia. Consequently, all other indications are beyond the remit of this appraisal.
	Royal College of Pathologists and British Society of Haematology	By not undertaking the MTA in the rare anaemias and transfused patients with Sickle cell disease this will promote discrimination of these groups as organisations that approve funding will say there is no NICE guidance. There is also no other clinical guidance these patients from the perspective of transfusional iron loading and hence have been treated similar to thalassaemia major for many years. The rarity of the rare anaemias makes it difficult to develop guidelines or specific treatment pathways. NICE should cover these as part of the thalassaemia guidance if this goes ahead.	An appraisal of treatment for chronic iron overload for conditions other than thalassaemia has not been referred to NICE by the Department of Health.
	ApoPharma Inc	There are no issues related to patient equality.	Comment noted.
	Eastern and Coastal Kent NHS	None.	Comment noted.
	NHS Northhampton shire	Satisfactory	Comment noted.

Section	Consultees	Comments	Action
	NHS Sickle Cell and thalassaemia Screening Programme	It may be considered that exclusion of patients with sickle cell from this analysis is inequitable. Effective chelation of transfusion dependent children and adults with sickle cell is an increasing activity within our clinics and the numbers of patients are going to be considerably higher than for thalassaemia major. It is acknowledged that the data available for a Technology Appraisal in the case of sickle cell disease is less and that this issue has already been discussed in preparing the scope	An appraisal of treatment for chronic iron overload for conditions other than thalassaemia has not been referred to NICE by the Department of Health.
	Novartis Pharmaceuticals UK	It is worth highlighting that deferasirox is used to treat chronic iron overload which, in the case of β- thalassaemia, occurs mainly in ethnic minority populations.	Comment noted.
	UK Forum on Haemoglobin Disorders	Only to repeat that the terms used in Background regarding ethnicity are not now those used.	The scope has been modified.
	United Kingdom Thalassaemia Society	The draft scope states that the population under examination is limited to: "People with thalassaemia major who have developed chronic iron overload following blood transfusions." The matrix of consultees and commentators includes Sickle Cell Anaemia but excludes all other Haemoglobinopathies affected by chronic iron overload such as MDS, DBA, Fanconi's Anaemia. It should be clarified why they have been excluded or, alternatively why only Sickle Cell Anaemia has been included in that list.	The Sickle Cell Society has been included in the matrix because thalassaemia is explicitly mentioned on their website and they also incorporate discussions on thalassaemia in their leaflets and booklets. Their scope therefore appears to extend to thalassaemia, which is the relevant population for this appraisal.
Other considerations	Commissioning Support Appraisals Service (CSAS)	None.	Comment noted.

Section	Consultees	Comments	Action
	Royal College of Paediatrics and Child Health	Guidance can extrapolate evidence in people with thalassaemia to other disease groups who need regular blood transfusions.	The appraisal will cover thalassaemia only, to reflect the remit received by NICE from the Department of Health.
	Royal College of Pathologists and British Society of Haematology	It is extremely important that if this scope goes ahead it also covers patients with transfusional iron overload with sickle cell disease, Blacken diamond anaemia, PK and G6PD deficiency, congenital sideroblastic anaemia and CDA.	An appraisal of treatment for chronic iron overload for conditions other than thalassaemia has not been referred to NICE by the Department of Health.

Section	Consultees	Comments	Action
	ApoPharma Inc	One of the questions for consultation related to combination therapy, whether it should be included in the technology appraisal and how it should be defined. The term “combination therapy”, as it relates to chelation in patients with thalassaemia, has been widely used ever since the original publication . Galanello has advocated that the term be restricted to the use of deferiprone and deferoxamine on the same day , but it is not always employed to refer to the use of the two chelators in this fashion. Sometimes, the use of the two agents in sequence (alternating therapy) is referred to as combination therapy. For the purpose of this review, it is suggested that combination therapy be employed for those situations in which deferiprone and deferoxamine are administered on the same days, whether or not administered at the same times. Deferoxamine need not necessarily be administered every day of the week, as this is not the case with monotherapy either. The dose of the two agents is typically tailored to the needs of the patient, and we would suggest that this approach be acceptable for the review as well, enabling a broad range of doses to be considered in the evaluation of combination therapy. Since the Exjade SmPC explicitly restricts its use to monotherapy (“The safety of Exjade in combination with other iron chelators has not been established. Therefore, it must not be combined with other iron chelator therapies”), the use of Exjade with either of the other two chelators would not be eligible for consideration as combination therapy. This should not be an issue in the evaluation as there are no comparative studies of the combination of Exjade plus another chelator against monotherapy with any chelator, although there is an interventional, non-randomized study currently listed in “ClinTrials.gov” (NCT00901199), that is examining the combination of Exjade and Desferal.	The ‘Other considerations’ section of the scope states that where the evidence allows, combinations of the different iron chelators will be considered.
	Eastern and Coastal Kent NHS	None.	Comment noted.

Section	Consultees	Comments	Action
	NHS Northamptonshire	Nil to add.	Comment noted.
	NHS Sickle Cell and thalassaemia Screening Programme	As above.	Comment noted.
	Novartis Pharmaceuticals UK	•It is worth noting that deferasirox was approved for use in patients with β-thalassaemia in NHS Scotland in 2007 and in NHS Wales in 2008. •Consideration should be given to the fact that there are social and cultural stigmas associated with this hereditary disease. The need for slow subcutaneous infusion of DFO via a visible balloon pump exacerbates this discrimination and leads to non-adherence, especially in the teenage population. •Non-adherence to treatment has a detrimental impact on morbidity and mortality. However there are no robust studies evaluating the effect of oral iron chelators on adherence and the longer term consequences of iron overload. There is likely to be better adherence to treatment with an oral chelator compared to one administered via subcutaneous infusion. This is supported by anecdotal evidence. •Special consideration should be given to the fact that deferasirox is the only oral chelator with a licence for the treatment of children between 2 to 5 years. In the absence of deferasirox, the only licensed option for this patient group is desferrioxamine and the potential quality of life benefits to these young patients of switching to deferasirox, an oral chelator, are important to consider.	Comments noted. The 'Other considerations' section of the scope states that where appropriate, treatment of children and adults will be considered separately.

Section	Consultees	Comments	Action
	United Kingdom Thalassaemia Society	One main area that has not been addressed sufficiently and would impose additional costs, but would equally provide considerable health benefits, is psychological support to the patient as well as to the family and carers when required. Ideally, it should be part of an integrated medical team and will improve QoL for the whole family.	The economic analysis will take into account all relevant costs and benefits associated with the technologies being appraised.
Questions for consultation	Commissioning Support Appraisals Service (CSAS)	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* All three treatments are currently approved for UK patients but the proposed technology appraisal should provide clarification on the relative long term effectiveness, tolerability and patient preference. The newer treatments deferiprone and deferasirox which can be taken orally may be preferable to the traditional infusion delivered chelator desferrioxamine. Attention should be given to assessing the effectiveness, safety and patient preference of combination therapy compared to monotherapy.	Comments noted.
		If appropriate, please include comments on the proposed process this appraisal will follow Desferrioxamine plus desferasirox and desferrioxamine plus deferiprone vs. monotherapy	The 'Other considerations' section of the scope states that where the evidence allows, combinations of the different iron chelators will be considered.

Section	Consultees	Comments	Action
	Royal College of Paediatrics and Child Health	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* The fact that deferasirox is the first, stand alone, likely effective treatment makes this an important step forward in technology, and appropriate to assess. The benefit looked for is medical efficacy at least as good as last technology (largely desferrioxamine) and acceptability/compliance with treatment that oral therapy (compared to parenteral) brings. We think that the Appraisal Committee needs efficacy data of all three treatments (singly and in combination) as well as acceptability and compliance data.	Comments noted.

Section	Consultees	Comments	Action
	Royal College of Pathologists and British Society of Haematology	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* At this time, with the iron chelation drugs having become PbR exclusions, the clinical situation is much better than previously with more equitable access to chelation therapy for patients. There is a valid concern that with clear guidelines already in place already by the Thalassaemia International Federation and the UKTS standards for care in thalassaemia that any NICE appraisal will not provide a meaning improvement in care for patients, as care in the Uk already follows clear well defined guidance (albeit from patient organisations). Indeed the opposite could happen. A high proportion of patients are established on regimes that suit them. If access to the drug (s) that they are now receiving, with effective iron control, became restricted as a consequence of the MTA, this could result in demotivation, loss of compliance and consequent increased morbidity and mortality. The MTA is therefore repeating work that has already been done and may not provide any significant meaningful improvement to the health care of patients with thalassaemia and other rare anaemias. For many patients, the availability of once daily 24h oral chelation, without the necessity for weekly blood monitoring has been a qualitative step change. *If appropriate, please include comments on the proposed process this appraisal will follow (please note any changes made to the process are likely to result in changes to the planned time lines).* If this MTA is to be clinically meaningful and provide improved evidence based care, patients with rare transfusion dependent anaemia's and sickle cell disease should be addressed.	This topic has been referred to NICE by the Department of Health as a Multiple Technology Appraisal of desferrioxamine, deferiprone and deferasirox for the treatment of chronic iron overload in people with thalassaemia. Consequently, all other indications are beyond the remit of this appraisal.

Section	Consultees	Comments	Action
		Evidence for the efficacy and safety of each chelation modality in young children should be included as a distinct issue. A more careful consideration of what 'combination therapy' means would also be helpful.	The 'Other considerations' section of the scope states that where appropriate, treatment of children and adults will be considered separately.
	ApoPharma Inc	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* Deferoxamine was the first treatment for iron overload for thalassaemia patients and had an impact on morbidity and survival, seen as early as the 1970's. Similarly, within three years of the launch of Ferriprox in Europe in 2000, the first publication noting decreased cardiac disease and increased survival was reported . Since this first report of evidence of cardioprotection and a trend towards increased survival was in a relatively small number of patients, little attention was paid to these findings initially. However, with the reports out of Italy comparing heart disease and survival in >500 patients on either Ferriprox or deferoxamine, showing a profound protective effect of Ferriprox in patients without any clinical evidence of heart disease , awareness of a major advance began accumulating. Similar benefits of reduced heart disease and increased survival were reported in Cyprus in >500 patients on Ferriprox plus deferoxamine, compared with deferoxamine alone . In that study, the hazard ratio for patients on combination therapy of 0.14 equates to 7.4-fold improved survival for each year on therapy. Most recently these observations were corroborated in the UK, where a 70% reduction was observed pursuant to the introduction of Ferriprox and the use of MRI T2* . We are unaware of any inherited disease where the magnitude of improvement in survival has been as impressive as that seen with Ferriprox in transfused patients with thalassaemia, supporting the view that this is indeed, a 'step-change' in therapy.	Comment noted.

Section	Consultees	Comments	Action
		Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* Thalassaemia is a chronic condition requiring life-long treatment with blood transfusions and subsequent iron chelation to prevent life threatening iron overload. Deferoxamine must be administered as a subcutaneous infusion over 8-12 hours, five to seven times per week. Given the intensive nature of this treatment regimen, adherence to treatment is often sub-optimal and the burden to both patients and parents/carers is substantial. Both of the orally available chelators have the potential to improve treatment adherence and ease the burden to the patient and caregiver. These intangible outcomes are difficult to include in a QALY calculation. To our knowledge no studies are currently available that quantify the burden of thalassaemia and iron overload management to the patient and caregiver. It is possible, however, that patient groups, such as the UK Thalassaemia Society and the Sickle cell society, could be approached to obtain quality of life data for patients and carers.	Comment noted. The benefits of oral versus subcutaneous infusion will be taken into account by in the appraisal.

Section	Consultees	Comments	Action
		Please answer any of the questions for consultation if not covered in the above sections. If appropriate, please include comments on the proposed process this appraisal will follow (please note any changes made to the process are likely to result in changes to the planned time lines). Two subgroups are raised as potential considerations-children and adults. As an inherited condition, patients with thalassaemia are treated from childhood throughout the rest of their life. The point at which one would draw a distinctive line of demarcation is unclear. Furthermore, to date, we know of no data which reports on different responses to any iron chelator in children as compared to adults, with the possible exception that young children can be "forced" to be compliant by their parents. Thus while we would not object to such a distinction, there are no data, of which we are aware, that would enable a distinction to be made. From an indication perspective, deferoxamine has no age restriction, whereas, the prescribing information for deferasirox states ("Exjade is indicated for the treatment of chronic iron overload due to frequent blood transfusions (≥7 ml/kg/month of packed red blood cells) in patients with beta thalassaemia major aged 6 years and older. Exjade is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contraindicated or inadequate in the following patient groups: - in patients with other anaemias, - in patients aged 2 to 5 years, - in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells).	The 'Other considerations' section of the scope states that where appropriate, treatment of children and adults will be considered separately.

Section	Consultees	Comments	Action
		While no age restriction is specified for Ferriprox, the SmPC, based upon data submitted to the EMA in 1998, notes the paucity of information regarding its use in young children ("There are limited data available on the use of deferiprone in children between 6 and 10 years of age, and no data on deferiprone use in children under 6 years of age"). Since that time, there has been considerable use in young children and a study of deferiprone in 100 children, aged 2-10 years old has recently been published . An update to the SmPC on the paediatric information is planned. This further argues against a distinction in evaluating the products on the basis of age.	
	Eastern and Coastal Kent NHS	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* All three treatments are currently approved for UK patients but the proposed technology appraisal should provide clarification on the relative long term effectiveness, tolerability and patient preference. The newer treatments deferiprone and deferasirox which can be taken orally may be preferable to the traditional infusion delivered chelator desferrioxamine. Attention should be given to assessing the effectiveness, safety and patient preference of combination therapy compared to monotherapy. *If appropriate, please include comments on the proposed process this appraisal will follow* Desferrioxamine plus desferasirox and desferrioxamine plus deferiprone vs. monotherapy	Comment noted.

Section	Consultees	Comments	Action
	NHS Northamptonshire	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* Yes.	Comment noted.
	NHS Sickle Cell and thalassaemia Screening Programme	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* Oral iron chelation, particularly with Deferasirox, a once daily oral agent, represents a major advance in chelation therapy. Data suggests efficacy and safety is acceptable, and the ease of administering compared to the previous standard therapy of sub cut desferrioxamine is so much better. Substantial health benefits are expected and it will be important to include quality of life analysis.	Comment noted. The benefits of oral versus subcutaneous infusion will be taken into account by in the appraisal

Section	Consultees	Comments	Action
	Novartis Pharmaceuticals UK	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* • The historical gold standard treatment for chronic iron overload is desferrioxamine. However it is administered as a slow subcutaneous infusion over 8 to12 hours for 5 to 7 days a week, and this demanding infusion regimen is problematic for most patients, interfering with sleep, limiting social activities and impacting significantly on daily life. It can be particularly distressing for children, some as young as two years of age, and for their parents or carers who must administer the infusion. • The inconvenience of parenteral administration of DFO, and associated AEs such as injection-site irritation and soreness, hinders optimal compliance. This parenteral administration has a negative impact on patients' quality of life and interferes with their ability to live normal lives. However, since the launch of deferasirox over four years ago, patients' quality of life has been improved because deferasirox is an effective, oral, once-daily iron chelation agent. In addition, it is the only iron chelator to provide continuous 24-hour reduction of toxic plasma iron, thereby protecting vital organs from iron damage. Due to the greater convenience of a once-daily oral administration, deferasirox has resulted in improvements in treatment satisfaction, adherence and quality of life in these patients compared to that achieved with DFO. • In addition, deferasirox has been shown to be effective in both chelation-naïve and chelation-experienced patients. • Deferasirox has a better side effect profile compared to deferiprone, the other oral chelator.	Comments noted. The other considerations section of the scope states that, if the evidence allows, the effect of adherence to treatment on outcomes will be considered.

Section	Consultees	Comments	Action
		Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Yes •The significant QOL improvements deferasirox will confer on parents or carers who otherwise have to ensure that children in their care adhere to DFO treatment, even when they are in discomfort, is not captured by the QALY •There is anecdotal evidence showing that there are social and cultural stigmas associated with DFO infusional treatment within ethnic minorities. These stigmas might be exacerbated in certain ethnic minority cultures. •The health benefits of eliminating the social and cultural stigma attached to continuous infusional regimes with DFO treatment when patients switch to deferasirox (an oral chelator that can be easily and privately taken) are not captured by the QALY. •Deferasirox brings potential freedom of movement, especially to young teenagers, who are able to enjoy their energetic lives without the hindrance associated with lengthy DFO infusions. Such indirect QOL benefits are not readily captured by QOL instruments such as the EQ-5D and hence the QALY.	Comments noted.

Section	Consultees	Comments	Action
		Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. **Technology benefits** Published data from RCTs as well as open label study extensions and non-comparator trials provide information demonstrating that: •deferasirox is an effective chelator, removing iron from the liver, heart and other organs. •deferasirox is well tolerated and has a good overall safety profile •deferasirox is effective in patients inadequately chelated with DFO due to poor compliance or contraindications •deferasirox improves patient satisfaction and health-related quality of life. •deferasirox can be used long-term without affecting paediatric growth **Benefits not captured by the QALY** •These benefits are best highlighted by patients and carers who experience the QOL benefits of an oral chelator versus an infusional chelator. We therefore suggest that NICE consults with relevant patient groups through its patient and public involvement programme (PPIP) so as to fully capture all the qualitative benefits not readily captured by the QALY.	Comments noted.

Section	Consultees	Comments	Action
		Is the population defined appropriately or should it be limited to beta thalassaemia major? The population should be limited to beta thalassaemia major. *What combination therapy should be included, and how should this be defined?* The combination therapy of deferiprone and DFO should be included as this has been shown to be effective in patients with significant cardiac iron overload (as indicated by a T2* measurement of, <6ms). *Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? For example, should patients with cardiac iron be considered separately?* The most important sub-groups are (a) children aged 2 to 5 years and (b) patients with significant cardiac iron overload (T2* of <6 ms) where deferiprone and DFO combination is appropriate. These sub-groups should be considered separately, for reasons explained earlier	Following consultation, the population in the scope is people with thalassaemia who have developed chronic iron overload following blood transfusions. The 'Other considerations' section of the scope states that where the evidence allows, combinations of the different iron chelators will be considered. The 'Other considerations' section of the scope states that where appropriate, treatment of children and adults will be considered separately.

Section	Consultees	Comments	Action
		Please consider whether in the remit or the scope there are any issues relevant to equality. Please pay particular attention to whether changes need to be made to the scope in order to promote equality, eliminate unlawful discrimination, or foster good relations between people who share a characteristic protected by the equalities legislation and those who do not share it, or if there is information that could be collected during the assessment process which would enable NICE to take account of equalities issues when developing guidance. The appraisal should recognise that thalassaemia is a condition common amongst ethnic minority populations who may be considered disadvantaged in society. In addition, this hereditary disease requires treatment of children as young as 2 years old. The appraisal should take into account the immense difference an oral treatment such as deferasirox will make to these children who would otherwise face years of DFO treatment that would substantially reduce their quality of life.	Comment noted. The 'Other considerations' section of the scope states that where appropriate, treatment of children and adults will be considered separately.
	UK Forum on Haemoglobin Disorders	These are established treatments, so in that regard not innovative, but the assessment will be valuable in guiding which agent is best used in which clinical circumstance, and in giving insight into quality of life comparators. Although there is a great deal of peer reviewed published research comparing the agents, opinions in the prescribing community still vary quite considerably and objective analysis will be valuable.	Comment noted.

Section	Consultees	Comments	Action
	United Kingdom Thalassaemia Society	Q. Is the population defined appropriately or should it be limited to beta thalassaemia major? A: The draft scope states that the population under examination is limited to: "People with thalassaemia major who have developed chronic iron overload following blood transfusions." In addition, there is a significant population of thalassaemia intermedia patients that can be both transfusion dependent as well as non transfusion dependent that do develop chronic iron overload and thus they also need to be included in the appraisal. We also question the reasoning behind the removal of other population groups who also need and depend on the same chelation therapy. Q. What combination therapy should be included, and how should this be defined? A: There is currently only one mode of combination therapy in extensive use, that between Desferrioxamine and Deferiprone. We are also aware or research been undertaken internationally, within the last 3 years between Deferiprone and Deferasirox.	The population has been amended to include thalassaemia intermedia. An appraisal of treatment for chronic iron overload for conditions other than thalassaemia has not been referred to NICE by the Department of Health. The 'Other considerations' section of the scope states that where the evidence allows, combinations of the different iron chelators will be considered.

Section	Consultees	Comments	Action
		Q. Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? For example, should patients with cardiac iron be considered separately? A: We do not believe there should be a restriction on the basis of marketing authorisation for several reasons: The Deferasirox marketing authorisation has been recently evolving to increasing doses (from 10-30mg/kg to 40mg/kg), as well as novel combination treatments not described in the original marketing authorisations are under investigation. Furthermore, we recommend that the appraisal should reflect clinical practices in terms of dosing beyond 'once daily' dosages that differ from the marketing authorisation in force. We do agree that patients with cardiac iron should be treated differently due to the fact that several studies are available that show different or even conflicting correlations between serum ferritin and myocardial iron loading as to liver iron concentration.	The 'Other considerations' section of the scope states that where the evidence allows, combinations of the different iron chelators will be considered. It also states that where the evidence allows, patients with significant cardiac iron overload will be considered as a subgroup.
		Q. Do you consider desferrioxamine, deferiprone and deferasirox to be innovative in their potential to make a significant and substantial impact on health-related benefits and how they might improve the way that current need is met (is this a 'step-change' in the management of the condition)? A: Yes, all of the chelators have played a role in making a significant and substantial impact on health-related benefits in different ways. In reducing organ damage and organ failure which in turn helped improve quality of life, self-image, self-confidence, societal perception as well as ability to lead a more normal, productive and assured life. With the advent of each one, clinicians have been provided with additional choices in managing iron overload and adherence.	Comment noted.

Section	Consultees	Comments	Action
		Q. Do you consider that the use of desferrioxamine, deferiprone and deferasirox can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? A: Yes. Improvements in health, outlook, lifestyles and the quality of life of patients with such a chronic condition, resulting from the gradual alleviation of the iron chelation burden, due to oral chelation, is allowing them to move towards becoming net economic contributors to society. This is not accurately captured in the QALY. Q. Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. A: The majority of these benefits are captured in published research showing improvements in survivability through the decades. Indicatively we recommend, Modell et al., Survival in beta thalassaemia major in the UK: data from the UK Thalassaemia Register, Lancet 2000; 355(9920):2051-2052 as well as Telfer et al., Quality of life in thalassaemia, Ann N Y Acad Sci 2005; 1054:273-82. Furthermore the UKTS Standards of Clinical Care of Children with Adults with Thalassaemia in the UK, 2008 also provide evidence of patient preferences in the corresponding chapter.	Comment noted. Comment noted.
Additional comments on the draft scope.	Royal College of Pathologists and British Society of Haematology	Treatment for patients is often very “fluid in nature” with changes in regimes happening across a lifetime dependant on the individual’s clinical needs. It is important that the MTA is not prescriptive or limiting the ability of clinicians to prescribe, based on individual patient needs and does not hinder the ability of clinicians to use their expertise to improve the health outcomes of individuals. The advantages of a flexible approach using the full range of chelators and diagnostic techniques available has been demonstrated in a recent audit of survival and cardiac disease in the two largest UK centres for thalassaemia care. Survival has improved dramatically and cardiac disease is no longer the leading cause of death (Thomas et al, Blood 116,21, abstract 1011)	Comment noted.

Section	Consultees	Comments	Action
	Eastern and Coastal Kent NHS	None.	Comment noted.
	NHS Northamptonshire	Satisfactory.	Comment noted.
	Novartis Pharmaceuticals UK	None.	Comment noted.
	United Kingdom Thalassaemia Society	None.	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Liverpool Reviews and Implementation Group (LRiG)
Department of Health
Royal College of Nursing
Welsh Assembly Government