Clinical Commissioning Policy: Treatment of iron overload for transfused and non transfused patients with chronic inherited anaemias

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Contact Details for further information	england.specialisedcommissioning@nhs.net

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Clinical Commissioning Policy: Treatment of iron overload for transfused and non transfused patients with chronic inherited anaemias

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Policy Statement

NHS England will commission the treatment of iron overload for transfused and non-transfused patients with chronic inherited anaemias in accordance with the criteria outlined in this document. In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources. This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About inherited anaemias

Inherited anaemias are passed down in families. They include:

- sickle cell disease
- thalassemia
- some other rare anaemias

They are blood problems affecting red blood cells. They need specific treatments.

About the current and future treatment

One of the treatments for inherited anaemias is to have blood transfusions - these temporarily increase the number of red blood cells.

- Some people need blood transfusions only now and then - such as when they are very unwell.
- Other people need regular blood transfusions over a long time.

Blood contains iron and one of the risks of having transfusions over a long time is getting too much iron in the body. As the body has no natural way to get rid of iron, repeated transfusions can lead to a build-up of iron in the body. This is called 'iron overload' and this can cause damage to different organs in the body.

The iron cannot be removed from the blood before transfusion. This is because it is an important part of 'haemoglobin'. This is a protein in red blood cells that carries oxygen.

Fortunately, iron overload and organ damage can be stopped with 'chelation therapy'.

- In chelation therapy, a medicine is used to remove metals like iron from the body.
- The medicine binds to the iron - the medicine and the iron then can pass out of the body. This is through the urine or stools.
- The medicines come in two forms that can be managed by the patient themselves. The first involves a needle and pump to give the medicine over an 8-24 hour period. The second involves taking oral tablets. Selecting the right treatment will depend on the clinical needs of the patient including how they can manage with taking the different types of medicine.

Doctors use MRI scans of the heart and liver to measure the amount of iron in the body before starting treatment and at regular intervals to check the treatment is working well.

What we have decided

NHS England has carefully reviewed the evidence for use of three chelation medicines and one combination of these

- Desferrioxamine (DFO)
- Deferiprone (DFP)
- Deferasirox (DFX)
- Combination on DFO and DFP

We have concluded that there is enough evidence to consider making all of these treatments available as treatment options for patients who have sickle cell disease, thalassaemia or rare inherited anaemias and who have iron overload (caused by transfusions) as set out in the commissioning criteria.

1 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission the treatment of iron overload in patients with inherited anaemias.

Inherited anaemia is an umbrella term to cover a number of haemoglobinopathies and other red cell disorders. Some haemoglobinopathies such as thalassaemia major (TM) are severe enough to require life-long blood transfusions whereas patients with non-transfusion-dependant thalassaemia (NTDT) and sickle cell disease (SCD) will require either intermittent, regular or no transfusions, dependent on disease severity and disease-related complications. Other inherited anaemias include Diamond Blackfan anaemia (DBA), Sideroblastic Anaemia (SA), Pyruvate Kinase deficiency (PKD), G6PD deficiency and rarer red cell membrane disorders, congenital dyserythropoietic anaemias and enzymopathies. These disorders may also require regular or intermittent transfusions to maintain an adequate haemoglobin level. Patients with NTDT and other rare anaemias may develop iron overload in the absence of blood transfusion simply from increased iron absorption from the gastrointestinal tract.

Blood transfusion therapy results in accumulation of iron, which is a key component of haemoglobin present in the red blood cells. Each unit of blood contains between 200-250 mg iron. The human body has no mechanism for removal of the iron and therefore patients who are regularly transfused will develop iron overload.
Before the advent of chelation therapy, a regularly transfused patient would develop serious life threatening complications and ultimately die as a direct consequence of iron overload. Iron chelation therapy removes the iron gained from blood transfusion or increased gastrointestinal iron absorption.

Iron overload causes serious complications in the endocrine system, the liver and the heart. Endocrine complications begin at a young age with irreversible damage to the pituitary gland resulting in growth retardation and failure of pubertal development. In adolescents and adults, endocrine damage results in gonadal failure, insulin-

dependent diabetes, hypopituitarism, hypothyroidism and hypoparathyroidism. Iron overload results in liver fibrosis, cirrhosis, liver cancer, cardiac failure, cardiac dysrhythmias and death. Heart disease is the commonest cause of death due to iron overload.

A patient who has iron overload will start chelation therapy with one agent but then may require various chelation regimens in their lifetime dependant on tolerability, complications with the drugs, and severity of iron burden as well as lifestyle issues.

There are currently three licensed iron chelation drugs: Desferrioxamine (DFO), Deferiprone (DFP) and Deferasirox (DFX). Their specific licensed indications differ. Both DFP and DFX are orally active, whereas DFO is usually given by subcutaneous infusion over 8-12 hours, 5-6 nights per week. Long-term adherence to chelation therapy is a requirement for efficacy and oral therapy has been shown to provide an advantage over sub-cutaneous treatment for some patients.

The aim of treatment is to adjust regimens to provide the most effective chelation with the optimal compliance. Iron chelation therapy has transformed the prognosis of these disorders, converting transfusion-dependant anaemias from fatal to chronic long-term conditions. With optimal treatment, patients have a normal life expectancy. Engaging patients through offering information about chelation options, checking understanding, and monitoring and communicating results, are important for good treatment adherence when selecting regimens based on individual clinical need and patient preference.

Achieving optimal outcomes depends on effective use of monitoring tests to modify chelation regimens to target both liver and cardiac iron. Serum ferritin is commonly used to monitor trends in iron burden and definitive quantitative tests have historically involved either tissue diagnosis using biopsy or magnetic resonance imaging (MRI) quantification.

A variety of MRI methods have been used to measure liver iron including

- R2-weighted spin-echo MRI (hereafter ‘R2-MRI’ or its reciprocal ‘T2-MRI’), with or without signal intensity ratios (SIRs) to adjacent tissues,

- R2* gradient-echo MRI (hereafter ‘R2*- MRI’ or its reciprocal ‘T2*-MRI’), with or without SIR.

In the UK R2* and SIR are not used outside of a research setting. Liver T2* is often assessed as part of the cardiac T2* MRI assessment and patients will be given a result for both cardiac and liver T2* assessment.

More recently, other techniques have been introduced specifically for LIC determination. Of these, the R2 technique using software application FerriScan®, registered in the European Union, is the most widely used and can be performed on a standard MRI scanner. Data generated from an R2-MRI scan of a patient’s liver is sent electronically to a commercial organisation (Resonance Health Ltd at www.ferriscan.com) where the software analyses the data using a calibration curve in order to generate an average liver iron concentration value. This approach, coupled with regular calibration of the MRI scanners at the sites using the technique, is designed to improve consistency in measurement and reporting across different centres.

Studies have focused on comparing which MRI technique should be used for the purpose of diagnosis and monitoring of both liver and cardiac iron overload. Quantitative tests are used to support targeted chelation therapy to help ensure both the liver and the heart are effectively cleared of iron. The gold standard for evaluation of total body iron load is measurement of the liver iron concentration (LIC) via chemical analysis of liver needle biopsy specimens. However, liver biopsy is invasive, potentially associated with significant complications, costly and subject to sampling error. MRI has emerged as the main non-invasive technique for quantification of iron in the liver and in the heart, where it is able to detect iron overload before iron toxicity becomes clinically apparent.

2 Definitions

Thalassaemia major (TM): Inherited severe anaemia due to absence or reduced production of either alpha or beta globin chains of haemoglobin. Almost all patients in

England with TM have forms of beta thalassaemia. Patients will require regular blood transfusions to support life.

Thalassaemia Intermedia (TI) or Non-Transfusion Dependent Anaemia (NTDT): Inherited moderately severe anaemia. Patients are either transfusion independent, intermittently transfused or regularly transfused but at a lower intensity.

Sickle Cell Disease (SCD): Patients who have the sickle beta globin mutation. Sickle cell disease is associated with a variety of both acute and chronic complications that can cause serious morbidity and many are on regular transfusion as part of their clinical management.

Rare anaemias: These include Diamond Blackfan anaemia, red cell enzymopathies and red cell membrane defects, Sideroblastic anaemia, congenital dyserythropoietic anaemias and other rarer anaemias.

Iron chelation therapy: This is the treatment given to patients to remove excess iron. There are 3 drugs currently used for iron chelation and they can be used as monotherapy or in combination to help control the iron burden.

Desferrioxamine (DFO): Iron chelation medication administered through a needle, inserted under the skin or via a central line such as a port-a-cath or PICC/Hickman line. It is administered through a pump that runs for between 8-24 hours. Patients have to take this treatment for 5 to 7 days a week as monotherapy or between 2 to 7 days a week as part of a combination therapy regimen.

Deferiprone (DFP): Oral iron chelation medication taken as tablets or syrup 3 times a day.

Deferasirox (DFX): Oral iron chelation medication currently administered as a dispersible tablet taken once daily.

Combination therapy: When more than one chelation drug are used as part of a treatment strategy. DFO and DFP are the two drugs most often used in combination.

Ferritin: This is a blood test used to monitor iron levels.

Magnetic resonance imaging (MRI): Used to monitor iron burden in both the liver and the heart to ensure that chelation is given in effective doses and identifies cardiac complications before the patient develops cardiac failure. Measurement of cardiac iron is done using the cardiac T2* and measurement of liver iron can be undertaken with T2*, R2* (inverse of T2*) or R2 (Ferriscan® methodology).

Left Ventricular ejection fraction (LVEF): This is a measure of how well the heart pumps. In cardiac failure the LVEF is reduced.

Cardiac Arrhythmia/ Dysrhythmia: Abnormal beating of the heart, which in these conditions usually reflects damage from cardiac iron loading.

Aplastic Anaemia, Myelodysplasia and haematological malignancies: These are bone marrow disorders for which a patient may require blood transfusions. These conditions are exclusions to this policy.

Haemochromatosis: An inherited disorder that results in iron overload. Occasionally patients need iron chelation therapy. This is condition is an exclusion to this policy.

Iatrogenic iron overload: Any iron overload that develops as a result of medication with iron containing preparations. This scenario is an exclusion to this policy.

LIC: Liver iron concentration

3 Aims and Objectives

To consider:

a) The evidence for the clinical effectiveness of Desferrioxamine in achieving control of iron levels and preventing complications of iron overload compared with monotherapy with Deferasirox or Deferiprone or combination therapy with Deferiprone and Desferrioxamine.

b) The evidence for the cost effectiveness of Desferrioxamine in achieving control of iron levels and preventing complications of iron overload compared with Deferasirox, Deferiprone and combination therapy with Desferrioxamine and Deferiprone.

c) The evidence for the clinical and cost effectiveness of chelation therapy in NTDT, compared with no chelation therapy, in achieving control of iron levels and preventing the complications of iron overload.

d) The evidence for the accuracy of currently available MRI methods in diagnosing and monitoring liver and cardiac iron overload.

The objectives were to:
e) Develop a policy for iron chelation for eligible patients (those with transfused and non-transfused chronic inherited anaemias) which supports regimen selection based on clinical presentation, adherence and monitoring requirements of individuals.

It was recognised that whilst iron chelation treatment in general is already routinely commissioned, there is some variation in access to all the regimens listed in this policy.

The recommendations here apply to those starting chelation or requiring a change of regimen due to toxicity or tolerability or to optimise chelation. This policy does not require the switching of those who are on regimens which already achieve the goal of chelation. The policy supports use of the commissioned regimens DFO, DFP and DFX monotherapy or DFO and DFP combination, according to the progress of the disease, so as to achieve the required goals of chelation, as deemed appropriate by clinicians and patients in the clinical setting.

4 Epidemiology and Needs Assessment

The inherited genetic changes leading to sickle cell disease (SCD) and thalassaemia are associated with an individual's ethnic origin. The prevalence of these disorders in

a population will therefore relate to the proportion of that population from susceptible ethnic groups as well as wider societal changes which mean that ethnicity alone may not be an accurate predictor of who might carry the trait or pass on the disorder.

Sickle Cell Disease (SCD)

The evidence review indicated that In the UK, about 12,500 people have SCD. It is more common in people whose family origins are African, African-Caribbean, Asian or Mediterranean. It is rare in people of North European origin. On average, 1 in 2,400 babies born in England have SCD, but rates are much higher in some urban areas - about 1 in 300 in some places (Patient, 2014).

Data from the National Haemoglobinopathy Registry (NHR) shows that about 80% of people with SCD are cared for at London centres with the remainder being largely confined to major cities such as Birmingham and Manchester. Approximately 9% of patients with SCD are on long term transfusion programs and about 40% of those transfused are currently receiving iron chelation. It is recognised that this data may be incomplete and underestimate the numbers on transfusion and on iron chelation.

The overall numbers of patients with SCD requiring transfusion and iron chelation are set to increase. This is in part because children <10 years of age form the largest group on the NHR and 10-15% of these need transfusions long term, because of raised trans-cranial Doppler (TCD) flow. In addition the ageing population of patients with SCD requiring long term blood transfusion have an increasing chronic disease burden with complications such as sickle renal, liver, heart and lung disease.

The need for iron chelation in adults will reflect the availability of automated red cell exchange transfusion which can be considered iron neutral. Recommendations in respective of red cell exchange are outside the scope of this policy.

Thalassaemia

The evidence review identified that Thalassaemia is more prevalent amongst Southern European, Middle Eastern, Asian and Southeast Asians. It is estimated to affect about 12 per 100,000 of the UK population, although the prevalence in some ethnic groups is substantially greater and the prevalence in any locality will be

affected by the proportion of the population that are genetically linked to susceptible populations (McLeod C, et al, 2009 and Roberts-Harewood M, 2009).

According to data from the NHR, distribution in the UK is different from SCD with a greater proportion of thalassaemia patients being treated outside London. There are an estimated 1500 patients in the UK of whom 947 are on the NHR (2014). According to the NHR, approximately half of these are on lifelong transfusions and around 60% are reported to receive iron chelation, the difference being a proportion of patients with non-transfusion dependent thalassaemia (NTDT) who can still develop complications due to iron overload. The improved life expectancy of patients with thalassaemia means that the prevalence in the UK, and correspondingly the need for iron chelation, will continue to increase. There are 20-30 new births of children with thalassemia per year in England.

There are also an unknown number of patients with rare inherited forms of anaemia who may require transfusion and/or iron chelation (estimated less than 500). These diseases are not population specific and are encountered across the UK. Clinical management is the same as for thalassaemia patients.

5 Evidence base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of these treatments for the indication.

Treatment

Based on the Population Intervention Comparator and Outcome (PICO) and search strategy, the evidence review concluded the following concerning iron chelation treatment:

- DFO and the oral iron chelators, DFP and DFX produce significant reductions in iron stores in transfusion-dependent, iron-overloaded people.
- All iron chelators produce significant reduction in liver iron in transfusion-dependent iron loaded people and there is no evidence to suggest one treatment is more efficacious than another. There is also no conclusive or

consistent evidence for the improved efficacy of combined DFP and DFO therapy over monotherapy for the reduction of liver iron.

- There is evidence from a meta-analysis showing significant improvement in cardiac function as, measured by Left Ventricular Ejection Fraction (LVEF) in favour of the DFO/DFP combination compared to DFO alone. There is also evidence that DFX is non-inferior to DFO in improving cardiac iron.
- There is evidence that adverse events are seen with all chelators but are increased in patients treated with DFP compared with DFO and in patients treated with combined DFP and DFO compared with DFO alone. Adverse events are also increased in DFX compared with DFO. Follow up in the available studies was too short to assess long term side effects of DFX.
- Cost effectiveness between injected and oral treatments is sensitive to the cost of the administration pumps. One analysis found DFP to be cost effective compared with DFO and DFX. There is evidence to suggest DFX is likely to be cost effective compared with DFO but not compared with DFP. Secondary analysis of DFX compared with combination therapy (DFO plus DFX) for highly iron-overloaded patients showed DFX to be slightly less cost-effective although mean ICER was still under 5,000.
- There is no published analysis of cost-effectiveness of iron chelation therapy in reducing iron overload in NTDT patients.

Efficacy

Iron burden in the liver reflects total body iron and iron in the heart is associated with increased mortality. It is therefore important to assess the effectiveness of chelating agents DFO, DFP, DFX and DFO/DFP combination at preventing iron accumulation in both the liver and the heart.

There have been three Cochrane reviews of the clinical effectiveness of DFO, DFP and DFX in people with transfusion-dependent thalassaemia and one Cochrane review of the clinical effectiveness of DFX in people with sickle cell disease (SCD) (Fisher SA et al, 2013, Fisher SA et al, 2009, Meerpohl JJ et all, 2012, Meerpohl JJ et all, 2014). There was significant heterogeneity in chelation dose, duration and monitoring tests used to assess response to treatment in the clinical trials included in these reviews precluding meta-analysis for many of the results.

In patients with TM, availability of all treatment options appears to offer equal efficacy in controlling liver iron. Combination of DFO/DFP appears to be more effective than DFO alone in reducing ferritin and cardiac iron.
In transfusion-dependent SCD patients, results from two studies showed greater serum ferritin reduction with DFO compared to DFX (mean difference 440.69µg/l (95% CI 11.73 to 869.64µg/l)). However, both studies were over a short period of time and used relatively lower doses than are currently used in clinical practice (Meerpohl JJ et all, 2014).

In patients with NTDT, one randomised controlled trial of DFX versus placebo reported that LIC decreased significantly compared with placebo (least-squares mean (LSM) ± standard error of the mean (SEM), -2.33 ± 0.7 mg Fe/g dry weight, P =0.001, and -4.18 ± 0.69 mg Fe/g dw, P <0 .001) for the 5 and 10 mg/kg/day DFX groups respectively. Serum ferritin decreased significantly compared with placebo (by LSM -235 and -337 ng/mL for the DFX 5 and 10 mg/kg/day groups, respectively (p< 0.001)) (Taher AT et al, 2012).

A meta-analysis of two studies noted significant improvement in cardiac function as measured by Left Ventricular Ejection Fraction (LVEF) in favour of the DFO/DFP combination compared to DFO alone (mean difference 6.22% (95% CI 4.32 to 8.12) (Fisher SA et al, 2013). Pennell compared DFX with DFO in patients with cardiac iron loading and found that DFX was not inferior to DFO in improving cardiac iron (Pennell DJ et al, 2014).

Safety

In the trials, adverse events were observed in all treatment groups. Adverse events were significantly less likely with DFO than DFP in one trial, relative risk (RR) 0.45 (95% CI 0.24 to 0.84), and significantly less likely with DFO alone than DFO combined with DFP in two other trials, RR 0.33 (95% CI 0.13 to 0.84). Permanent treatment withdrawal due to adverse events was higher with DFP than with DFO. The most commonly reported adverse event with DFP was joint pain, this occurred more frequently than with DFO, RR 2.64 (95% CI 1.21 to 5.77). Other common adverse events with DFP included gastrointestinal disturbances, neutropenia and/or a low

white cell count. The most commonly reported adverse event with DFO was reaction at the injection site.

Adverse events also occurred at a higher frequency in patients who received DFX than DFO in one trial; however there was no difference in serious adverse events.

Patient satisfaction was significantly better with DFX, but rate of discontinuations was similar for both drugs. Regular monitoring of white cell counts has been recommended for DFP and monitoring of liver and renal function for DFX (Fisher SA et al, 2013, Fisher SA et al, 2009, Meerpohl JJ et al, 2012, Meerpohl JJ et al, 2014).

Impact on Quality of life

All three chelators may cause adverse effects (AEs), though the spectrum is different for each. Systematic monitoring for AEs is an essential part of iron chelation management. The tolerability of a particular chelator and its AEs as experienced by each individual patient will be a major factor in determining whether the drug is a good choice for long-term therapy for that individual. This requires assessment, regular monitoring and a good therapeutic relationship between the specialist and the patient.

In addition to the search strategy for the evidence review, the Clinical Reference Group identified the following data on Quality of life (QoL), an area in which there is little published data:

- In general, adolescents and adults with thalassemia report worse QoL than the general population, despite the availability of a variety of chelation regimens (Sobota A et al, 2011)
- A Greek study suggested adherence to treatment was the lowest in the DFO group compared to the DFX group and the DFO + DFP group. More patients receiving DFO (19%) felt that their treatment was hard or very hard to receive compared to 6.7% for DFX and 5.1% for DFO + DFP. This is in contrast to 9.5%, 42.7%, and 38.2% of those receiving DFO, DFX, and DFO + DFP, respectively, who felt that receiving their therapy was easy or very easy (Goulas V et al, 2012)

- Mazzone reported that 90% of TM children complied well with chelation therapy but had significantly increased somatic complaints, physical symptoms, separation panic, as well as high emotionality and low sociability necessitating psychological support to facilitate adherence to iron chelation and to contain the emotional burden (Mazzone L et al, 2009)
- The self-reported adherence to the iron chelation treatment is correlated with age, gender, age at the start point of the treatment and emotional distress (Goldbeck L et al, 2000)

Cost-Effectiveness

The evidence review found four cost-effectiveness studies based on a UK health services perspective.

One cost-utility analysis found that DFX is likely to be more cost effective than DFO for iron overload in thalassaemia, at a QALY threshold of £20,000.

A cost-effectiveness analysis of DFX versus DFO and DFP in TM and SCD found that DFX may be more cost effective than DFO, depending upon age of the patient and use of balloon infusers for administration of DFO. However, DFX was unlikely to be cost-effective compared with DFP.

Another cost-utility analysis found that although DFX patients incurred greater acquisition costs, these were offset by the avoidance of infusion-related equipment costs. Compared with DFO, DFX dominated costs less and produced a greater gain in QALYs.

In the sensitivity analysis, the incremental cost-effectiveness ratio (ICER) was most sensitive to the equipment costs associated with the administration of DFO. In the worst case scenario analysis of 25% of DFO patients receiving DFO via balloon pump (the most expensive method) dominance was lost but the ICER remained below £20,000 per additional QALY gained. Secondary analysis of DFX compared to combination therapy (DFO+ DFX) for highly iron-overloaded patients showed DFX to be slightly less cost-effective although mean ICER was still under £5,000.

A further study assessed the cost-effectiveness of DFP compared with other treatments for iron overload in thalassaemia and found that DFP was dominant in all scenario analysis (McLeod C et al, 2009; Karnon J et al, 2008; Karnon J et al, 2012; Bentley A et al, 2013; Cappenllini MD et al, 2006; Cappenllini MD et al, 2011).

Monitoring

With regard to liver and cardiac iron monitoring, the evidence review concluded:

- There is a lack of high quality studies investigating the diagnostic accuracy of MRI for liver iron overload. However, current evidence suggests that MRI techniques may be sensitive enough to rule out iron overload in patients with haemoglobinopathies or rare anaemias; their specificity is slightly lower, which means they may be less accurate in establishing a definite diagnosis of liver iron overload.
- There is no evidence to suggest that cardiac T2-MRI offers any advantages over the existing reference standard, cardiac T2*-MRI, for the measurement of cardiac iron in patients with β-thalassaemia, sickle cell disease or other transfusion-dependent anaemias. There is also evidence to support the continued use of T2*-MRI in the measurement of cardiac iron overload in transfusion-dependent patients.

<u>Efficacy</u>

A variety of MRI methods have been used to measure liver iron including

- R2-weighted spin-echo MRI (hereafter 'R2-MRI' or its reciprocal 'T2-MRI'), with or without signal intensity ratios (SIRs) to adjacent tissues,
- R2* gradient-echo MRI (hereafter 'R2*- MRI' or its reciprocal 'T2*-MRI'), with or without SIR.

In the UK R2* and SIR are not used outside of a research setting. Liver T2* is often assessed as part of the cardiac T2* MRI assessment and patients will be given a result for both cardiac and liver T2* assessment.

Continuous use of the same technique allows trends to be monitored over time.

Liver iron overload:

Two studies have compared R2-MRI (Ferriscan®) with liver biopsy iron concentration. The 2005 study involved 105 patients with mixed diagnoses, of whom 50 had haemoglobinopathy or rare anaemia; only nine, with β-thalassaemia, were on regular transfusions and chelation therapy. The method of patient selection was clear but there was no reported blinding of the MRI observers to the liver biopsy results, so introducing the potential for observer bias (St Pierre TG et al, 2005). The 2014 study was larger, involving 233 patients with β- thalassaemia on regular transfusions and chelation therapy. Although the method of patient selection was not clear, the study appears to have been methodologically sound in other respects, such as the blinding of MRI reviewers. The study populations in both studies had a similarly wide range of liver iron concentrations (St Pierre TG et al, 2014).

Both studies showed that, in patients with β- thalassaemia, liver R2-MRI is correlated with liver biopsy iron across a wide range of liver iron concentrations (0.3 to 47.2 mg Fe/g dw liver in the 2005 study; 0.7mg to 50.1 mg Fe/g dw liver in the 2014 study). The earlier study reported sensitivity and specificity of R2-MRI for predicting biopsy LIC at each of four clinically important positivity thresholds: 1.8 mg Fe/g dw liver (the upper 95% limit of normal for LIC); 3.2 mg Fe/g dw liver (the suggested lower limit of the optimal range of LICs for chelation therapy in transfusional iron overload), 7.0 mg Fe/g dw liver (the suggested upper limit of the optimal range of LICs for transfusional iron overload and the threshold for increased risk of iron-induced complications), and 15.0 mg Fe/g dw liver (the threshold for greatly increased risk for cardiac disease and early death in patients with transfusional iron overload). At these thresholds, both sensitivity and specificity of R2-MRI were high, with sensitivity ranging from 0.85 to 0.94 and specificity from 0.92 to 1.00.

R2 MRI assessments (Ferriscan) are quality controlled with centralised reporting by Resonance Health. Therefore an assessment of liver iron undertaken anywhere in the UK will give the same result.

Two studies have compared liver R2*-MRI with liver biopsy iron concentration in samples of fewer than 50 patients in whom the most common diagnosis was sickle cell disease. In both studies, liver R2*-MRI was found to be significantly correlated

with liver biopsy iron concentration. In one, the correlation was strongest at lower liver iron concentration and progressively decreased with higher liver iron concentration values (especially >25 mg Fe/g dw liver, with the upper limit of iron concentration in the study population being 27.6 mg Fe/g dw liver) (McCarville MB et al, 2010). In the other, none of the patients had liver iron concentration higher than 17.7 mg Fe/g dw liver (Hankins JS et al, 2009). Therefore, neither study involved a study population representing the full spectrum of patients with iron overload, nor did they specify how patients were selected for study. The studies had some methodological strengths in that all patients underwent both index test (MRI) and reference test (liver biopsy), and both involved blinding of MRI reviewers to clinical status and/or liver biopsy results so reducing the potential for observer bias.

A systematic review and meta-analysis on the accuracy of MRI in the diagnosis of liver iron overload included 20 studies, published between 2001 and 2014, involving a total of 819 patients (Sarigianni M, et al, 2014). The systematic review was well conducted. For every included study, data was extracted to reconstruct 2 × 2 tables for each of three clinically relevant liver iron concentration (LIC) values and the corresponding MRI positivity thresholds. The selected LIC values - LIC greater than 2mg Fe/g dw liver indicated a diagnosis of iron overload, greater than 7 mg Fe/g dw liver suggested an increased risk for iron-induced complications and was the threshold used to initiate or intensify chelation therapy, and greater than 15 mg Fe/g dw liver was associated with a substantial risk for cardiac disease and early death – were derived Olivieri et al (1997). The sensitivity and specificity was estimated for each individual study and hierarchical models were used to depict summary receiver operating characteristic (SROC) curves.

All studies included in the review were considered to be at high risk of bias. In the main analysis, involving 17 studies, MRI sensitivity ranged from 0.00 to 1.00 (median 0.94); specificity ranges from 0.50 to 1.00 (median 0.89). However, because of substantial heterogeneity between the included studies, the reviewers were only able to pool results and present an SROC curve in subgroup analyses of studies using the same MRI sequences (T2-MRI and T2*-MRI) at an LIC threshold of greater than 7 mg Fe/g dw liver.

Both MRI sequences were shown to have good diagnostic accuracy (for T2-MRI, sensitivity 0.90 (95% CI 0.85 to 0.94), specificity 0.87 (0.76 to 0.93); for T2*-MRI, sensitivity 0.96 (95% CI 0.87 to 0.99), specificity 0.80 (0.53 to 0.94)) in identifying patients at risk of iron-induced complications or requiring titration of chelation therapy (threshold >7 mg Fe/g dw liver); prevalence was a significant predictor of sensitivity and specificity. Conditional probability plots were used to demonstrate the clinical utility of the two MRI sequences in detecting patients with LIC greater than 7mg Fe/g dw liver. The results suggested that both MRI sequences are likely to be more accurate at identifying patients without liver iron overload (negative likelihood ratio (NLR) 0.10 and 0.05 respectively) and less accurate in establishing a definite diagnosis of liver iron overload (positive likelihood ratio (PLR) 8.85 and 4.86 respectively).

The systematic review authors highlighted the paucity of high quality studies designed to investigate the diagnostic accuracy of MRI for liver iron overload and the importance of conducting future trials which use a more rigorous methodology, have a larger sample size, focus on specific MRI sequences and which use explicit positivity thresholds. They also reported that only two studies investigated the diagnostic accuracy of R2-MRI (Ferriscan; Resonance Health Ltd) in patients with iron overload and suggested that further evidence is needed to confirm the accuracy of this protocol.

Cardiac iron overload

In a review of the evidence conducted for the development of this policy, five studies (Kim D et al, 2011; Cheung JS et al, 2011; Song R et al, 2007; Feng Y et al, 2013; He T et al, 2009) were found which compared the reference standard for measurement of cardiac iron, T2*-MRI, with alternative MRI techniques for measurement of cardiac iron, in patients with haemoglobinopathies. Three studies involved fewer than 15 patients and no control group, so were not considered further.

Two studies each involved more than 100 patients and both compared cardiac T2-MRI with T2*-MRI in patients with beta- thalassaemia who were receiving regular transfusions and chelation therapy, and had a wide range of liver iron concentrations. Both included some methodological weaknesses including a lack of description as to how patients were selected for study and no blinding of MRI reviewer, so introducing

the potential for bias, but both demonstrated a strong correlation between cardiac T2-MRI and T2*-MRI for the sub-group of patients with myocardial iron, but no correlation between the two measures for patients with normal myocardial iron. One study also showed a strong correlation between cardiac T1-MRI and T2*-MRI for patients with myocardial iron. Further evidence has shown that R2*-MRI (and hence T2*) is strongly correlated with in vitro measurements of cardiac tissue iron taken from 12 human hearts of transfusion-dependent patients.

Safety

As MRI does not involve ionising radiation, it is generally viewed as a safe imaging modality as long as proper precautions are taken. There is also no evidence of a cumulative effect on health due to repeated MRI investigations and the repetitive exposure to magnetic fields. The main established hazard of MRI is the so-called 'projectile' or 'missile effect' in which, due to the large gradient magnetic field, ferromagnetic objects inadvertently entering the field are accelerated and become dangerous projectiles. Most reported cases of MRI-related injuries are due to mis-information relating to safety aspects of the MRI environment. They include projectile and burn incidents, altered function of devices (e.g. cardiac pacemakers), and the presence of unknown foreign metal objects. Adverse effects associated with MRI include sensory effects such as nausea, vertigo, and metallic taste. There is no reason to believe that different MRI techniques will have differing safety profiles, although the potential for adverse effects associated with the use of higher magnetic field strengths may need further research (Bulfone L et al, 2010).

By comparison, liver biopsy is an invasive and painful procedure which carries the risk of bleeding, infection, and damage to the liver or surrounding organs. Deaths associated with liver biopsy have been reported rarely. The safety of liver biopsy is enhanced by the use of ultrasound guidance; one large study, in patients with thalassaemia, reported a complication rate of 0.5%. The assessment of LIC by MRI is therefore highly likely to offer safety advantages when compared with liver biopsy (Angelucci E et al, 1995).

Cost effectiveness

The R2 technique FerriScan® is estimated to cost around £150 more per scan than other MRI techniques used in the investigation of iron overload. No other information on costs or activity associated with MRI techniques used in the investigation of iron overload was available at the time of the evidence review.

Equity issues

Cardiac T2*-MRI is the standard approach to measurement of cardiac iron load in England, whereas liver iron load is measured using either R2-MRI (T2) or T2*-MRI (R2*).

The evidence review also concluded that if a particular technique for measuring liver iron load is more accurate than another in use in another treatment centre, then patients who have access to the less accurate MRI investigation may, on the basis of its results, receive sub-optimal chelation therapy regime and be more at risk of adverse effects associated with iron overload and/or chelation therapy. R2 assessments are subject to a quality control and validation process that in house T2* techniques are not. However, the evidence review found that both R2 and R2* can accurately measure hepatic iron concentration with appropriate MRI acquisition techniques in equal capacity.

6 Criteria for Commissioning

The sequence of treatment selection will be determined by individual patient assessment for toxicity, tolerability and adherence in order to achieve the outcome of managing iron loading.

Patients starting iron chelation are likely to start on monotherapy. Where a patient is unable to tolerate monotherapy, an appropriate regimen will be selected by the clinician in partnership with the patient.

Therefore, this policy confirms Desferrioxamine (DFO), Deferiprone (DFP), Deferasirox (DFX) or Combination therapy (DFO and DFP) are commissioned as clinically indicated for the following indications:

Iron chelation therapy Indications:

- Transfusional iron overload in patients with inherited haemoglobinopathies or rare anaemias who either are on or have previously been transfused either regularly or intermittently; or
- Patients with non transfusion dependant inherited anaemia who have iron overload as documented by baseline scan or an MRI (liver iron of above 5 mg/g/dw as measured by R2 MRI or T2* liver iron assessment less than 5 ms at initiation of chelation or persistently raised ferritin (e.g. usually >800 ug/l) if the patient is unable to undergo an MRI assessment, and
- Patients and carers have been involved in decisions around chelation regimens to optimise adherence. This will include information about treatment schedule options, side effects and goals of the regimes proposed and confirming patients / carers understand the options discussed.

Exclusions:

- Combination therapy using Deferasirox (DFX) are excluded from this policy and are not routinely commissioned. However, it is recognised that the evidence base for other chelator combinations is changing and more information will emerge with regard to safety, efficacy and tolerability of these newer combination.
- Patients with transfusional iron loading due to other conditions such as aplastic anaemia, myelodysplasia, and haematological malignancies.
- Patients with iron overload for other reasons such as hereditary haemochromatosis or iatrogenic iron overload.

Starting and stopping criteria for chelation treatment:

Starting:

- Patients must be children or adults with TM or SCD or rare anaemias who are receiving regular blood transfusions.

- In NTDT patients with iron overload, chelation may be started when liver iron level is >5mg/g dw as measured by baseline scan or Ferriscan or T2* liver iron assessment less than 5 ms or persistently raised ferritin (e.g. usually >800 ug/l) if the patient is unable to undergo an MRI assessment. If a patient with NTDT starts a transfusion regime their chelation should be similar to that of a regularly transfused patient.

Stopping:

- Where transfusions are stopped, chelation therapy will continue until the iron burden returns to safe levels.
- Patients with normal iron burden but continuing transfusions will require doses commensurate with iron loading. NTDT patients may stop once iron levels <5mg/gdw but will require regular monitoring for accumulation and will need to resume chelation if levels >5mg/gdw

MRI for monitoring of cardiac and liver iron

Cardiac iron monitoring using T2* MRI and R2 MRI for liver iron monitoring for TM and other chronic anaemias.

Baseline scans should be undertaken for both cardiac and iron liver concentration and then frequency should be determined based on clinical presentation assessment depending on cardiac and liver concentrations and intensity of treatment.

- 6 monthly for severe cardiac iron loading (<10 msec)
- Every 1 – 2 years for stable patients with satisfactory iron levels
- As required for those with elevated LIC and / or mild to moderate cardiac iron.

Where patients are unable to be scanned due to claustrophobia, treatment will be guided by individual circumstance based on transfusion history and ferritin levels.

7 Patient Pathway

The oversight of iron chelation therapy is a responsibility of specialist haemoglobinopathy centres (SHC); this includes decisions about starting, monitoring,

changing and stopping therapy.

Provision of chelation may be provided at either the SHC or a local haemoglobinopathy centre or accredited local Haemoglobinopathy centre as part of network arrangements and agreed by the local commissioner.

Initiation and modification of chelation regimes should be undertaken by a SHC or A-LHC; however, chelation drug dispensing and prescription can and should occur at the centre where the patient normally is transfused.

8 Governance Arrangements

The governance arrangements are set out in the Specialised Services for Haemoglobinopathy Care service specification.

Recommendations relevant for this review include:

- The SHC should provide (or delegate) cardiac and liver MRI where indicated
- The SHC is responsible for the management of complex patients using a multidisciplinary team approach. Indicators of complexity relevant for this review include endocrine complications and cardiac complications related to iron overload
- The haemoglobinopathy dashboard includes measures for the monitoring of iron and this policy will be monitored through the dashboard measures.

The National Haemoglobinopathy Registry collects data on patients receiving iron chelation including drugs prescribed, complications and imaging assessments. This provides a mechanism for collecting the required data for the quality dashboards and for the numbers of patients on iron chelation.

9 Mechanism for Funding

NHS England commissions all care provided by SHCs where the cause of the admission is related to haemoglobinopathy. This includes services delivered on an

outreach basis as part of a provider network. Clinical Commissioning Groups (CCGs) commission all other care provided outside of SHCs.

Where shared care arrangements exist, the initiation of iron chelation therapy must be undertaken by, or under the supervision of, the SHC. Non-specialised providers may then take on responsibility for prescribing maintenance therapy, but only to agreed protocols, as part of a formal shared-care arrangement. Invoicing for iron chelation drugs from SHCs and local centres will be subject to local arrangements and agreements.

With the exception of excluded drugs, all clinical care related to haemoglobinopathy is included within HRG (health care resource group) tariff prices, and is funded via routine HRG reporting. This includes all MRI scans and other investigations. The costs of drugs excluded from tariff prices are funded as pass-through payments by commissioners, and no administration charges may be added by the SHC.

NHS England commissions the following excluded drugs for iron chelation in line with the criteria set out in this commissioning policy proposition:

- Deferasirox
- Desferrioxamine
- Deferiprone
- Deferiprone and desferrioxamine combination

10 Audit Requirements

1. The number of patients with TM, SCD ,NTDT and Rarer Anaemias on iron chelation
2. Chelation regimens used by indication
3. Number of patients with iron overload in mild, moderate and severe categories
4. Number of patients with cardiac iron overload in mild, moderate and severe categories.

Existing data collections routes (quality dashboard / National Haemoglobinopathy Registry) to be used where appropriate..

11 Documents which have informed this Policy

Documents used are set out in the evidence review.

12 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

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