

Diagnosis and monitoring of iron overload in patients with haemoglobinopathies or rare anaemias

QUESTION(S) TO BE ADDRESSED:

1. For all patients, transfused or non-transfused, who have haemoglobinopathies or rare anaemias and who might have iron overload, what is the accuracy of currently available magnetic resonance imaging (MRI) methods in diagnosing and monitoring liver iron overload compared with liver biopsy?
2. For all patients, transfused or non-transfused, who have haemoglobinopathies or rare anaemias and who might have iron overload, what is the accuracy of MRI methods (other than cardiac T2 star MRI) in diagnosing and monitoring cardiac iron overload compared with cardiac T2 star MRI (T2*-MRI)?

SUMMARY:

• **Background**

Patients with haemoglobinopathies, such as β -thalassaemia and sickle cell disease (SCD), and other transfusion-dependent anaemias usually require regular blood transfusions which leads to iron accumulation in the heart and liver. Iron chelation therapy is used to prevent iron toxicity but requires close monitoring of body iron levels to ensure optimal dosage and avoid potential adverse effects of excess chelator treatment. 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.

Magnetic resonance imaging (MRI) has emerged as the main non-invasive technique for quantification of iron in the liver and in the heart, where MRI is able to detect iron overload before iron toxicity becomes clinically apparent. MRI techniques currently used in the measurement of liver iron include R2-MRI (or its reciprocal T2-MRI), and R2*-MRI (or its reciprocal T2*-MRI). T2*-MRI is the accepted reference standard, for measurement of cardiac iron. Questions remain as to which MRI technique should be used for the purpose of diagnosis and monitoring of both liver and cardiac iron overload.

• **Evidence on diagnostic accuracy**

Liver iron overload

Three of the five individual studies included in this review showed that liver T2*-MRI (or R2*) is correlated with liver biopsy iron concentration. Two of the studies involved small study populations in whom the predominant diagnosis was sickle cell disease and liver iron concentrations (LIC) were less than 28 mg Fe/g dw liver; in one of these studies, the correlation was weaker with increasing liver iron concentration. The third study, in patients with a predominant diagnosis of β -thalassaemia and liver iron concentrations up to 42.3 mg Fe/g dw

liver, showed high correlation between liver T2*-MRI (R2*) and liver biopsy iron concentration. None of these studies published information to enable assessment of diagnostic accuracy of the MRI techniques at pre-specified, clinically important LIC thresholds.

Two studies by St Pierre (in 2005 and 2014) showed that, in patients with β -thalassaemia, liver R2-MRI is correlated with liver biopsy iron across a wide range of liver iron concentrations (0.7mg to 50.1mg Fe/g dw liver in the 2014 study). The earlier St Pierre 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 (suggested upper limit of normal for LIC); 3.2 mg Fe/g dw liver (suggested lower limit of the optimal range of LICs for chelation therapy in transfusional iron overload); 7.0 mg Fe/g dw liver (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 (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. The larger and more methodologically sound study, in 2014, did not publish information to enable estimation of the diagnostic accuracy of the MRI technique at pre-specified LIC thresholds.

A recent, well conducted systematic review and meta-analysis of 20 individual studies found that sensitivity of MRI ranged from 0.00 to 1.00 (median 0.94) and specificity ranged from 0.50 to 1.00 (median 0.89) at an LIC threshold of greater than 7 mg Fe/g dw liver. Subgroup analyses of T2 (SE) and T2* (GRE) showed that both MRI sequences have good diagnostic accuracy for identifying patients at risk of iron-induced complications or requiring titration of chelation therapy (>7 mg Fe/g dw liver). Further analyses suggested that both MRI sequences are likely to be more accurate in 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).

Cardiac iron overload

Both the Feng and He studies compared cardiac T2-MRI with T2*-MRI in patients with β -thalassaemia who were receiving regular transfusions and chelation therapy, and had a wide range of liver iron concentrations. Both studies 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. The Feng study also showed a strong correlation between cardiac T1-MRI and T2*-MRI for patients with myocardial iron.

Two studies were identified which compared cardiac T2-MRI and T2*-MRI in patients with β -thalassaemia. Both studies, which had some methodological weaknesses, showed strong correlation between cardiac T2-MRI and the existing reference standard for measuring myocardial iron, cardiac T2*-MRI.

• **Safety**

MRI is generally viewed as a safe imaging modality and different MRI techniques are unlikely to have differing safety profiles. 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. The assessment of LIC by MRI is therefore likely to offer safety advantages when compared with liver biopsy.

- **Activity and Cost**

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 writing this report.

- **Equity**

Cardiac T2*-MRI is the standard approach to measurement of cardiac iron load in England; liver iron load is measured using R2-MRI (T2) or T2*-MRI (R2*). If one technique for measuring liver iron load is more accurate than another, patients who access the less accurate MRI investigation may receive sub-optimal chelation therapy regime and be more at risk of adverse effects associated with iron overload and/or chelation therapy.

For public consultation

1 Context

1.1 Introduction

The routine management of patients with haemoglobinopathies, such as β -thalassaemia and sickle cell disease (SCD), and other transfusion-dependent anaemias involves the administration of regular blood transfusions. This leads to the gradual accumulation of iron in various tissues including the heart, liver and endocrine glands. Without aggressive iron chelation therapy, patients die from endocrine, liver and cardiac complications. Heart failure is the most common cause of death in β -thalassaemia and primarily results from cardiac iron accumulation [1].

Chelation therapy is life-saving but requires close monitoring of body iron levels to prevent iron toxicity and avoid the potential adverse effects of excess chelator treatment. The easiest and cheapest methods available for assessment of body iron levels are biochemical measurements of serum iron concentration, serum ferritin concentration and transferrin saturation. However, these biochemical tests can be confounded by inflammation and malignancy, so provide inaccurate estimates of total body iron in some patients. The gold standard for evaluation of body iron load in systemic iron overload is measurement of the liver iron concentration (LIC) via chemical analysis of liver needle biopsy specimens.

Liver biopsy is invasive, costly and subject to sampling error. To counter the shortcomings of liver biopsy, a number of alternative non-invasive techniques have been developed for estimation of liver iron, including biomagnetic liver susceptometry (BLS) based on the superconducting quantum interference device (SQUID)¹ and magnetic resonance imaging (MRI). MRI, which is more widely available than BLS, has emerged as the main non-invasive technique for quantification of iron in the liver and in the heart, where MRI is able to detect iron overload before iron toxicity becomes clinically apparent. Recently, both cardiac and liver iron levels measured using MRI have become the primary outcome measures used in clinical studies of iron chelation therapy [2]. However, questions remain as to which MRI technique should be used for this purpose (see section 3 for further details).

1.2 Existing national policies and guidance

There is no NICE guidance on the use of MRI in the diagnosis and/or monitoring of iron overload in patients with haemoglobinopathies or other transfusion-dependent anaemias.

In 2008, the United Kingdom Thalassaemia Society published 'Standards for the clinical care of children and adults with thalassaemia in the UK' [3]. In relation to the monitoring of iron overload, the guidelines state that: 'All patients should have access to MRI modalities (cardiac T2* MRI and either R2 or T2* of liver) for monitoring myocardial and liver iron.'

In 2013, the American Heart Association published a consensus statement on cardiovascular function and treatment in β -thalassaemia major in which it recommends the use of cardiac T2* MRI in the estimation of cardiac iron [1].

2 Epidemiology

Thalassaemia is more prevalent amongst Southern European, Middle Eastern, and African populations. It is estimated to affect about 12 per 100,000 of the UK population, although the

¹ The susceptometric technique entails measurement of magnetic field variations produced in the region of the liver in response to an external magnetising field.

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 [4,5].

In the UK, about 12,500 people have sickle cell disease (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 [6].

2.1 Iron overload in thalassaemia

In studies involving thalassaemia patients with post-transfusional iron overload, the prevalence of severe iron overload (liver iron concentration (LIC) greater than 14 mg Fe/g dw liver²) determined by biopsy was found to be around 40% [7,8].

The AHA consensus statement on cardiovascular management of patients with β -thalassaemia major includes data on the prevalence of cardiac iron overload in samples of patients from different countries [1]. Severe cardiac iron loading is defined as less than 10 milliseconds, measured using cardiac T2*-MRI, and mild to moderate cardiac iron loading is defined as 10 to 20 milliseconds. The data, shown in Table 1, suggest that cardiac iron overload is common in patients with β -thalassaemia major. In the UK sample of 109 patients [9], 20% of patients had severe cardiac iron overload and a further 43% had mild to moderate cardiac iron overload.

Table 1. Frequency of Cardiac Iron Overload

Country	Sample Size, n	Frequency, %		
		Severe: T2* <10 ms	Mild to Moderate: T2* >10–20 ms	Normal: T2* >20 ms
United Kingdom ⁵	109	20	43	37
Hong Kong ³³	180	26	24	50
Turkey ³⁴	28	46	39	14
Australia ³⁵	30	37	27	37
Oman ³⁶	81	24	22	54
United States ³⁷	141	13	21	66
Italy ³⁸	167	13 (<8 ms)	52 (8–20 ms)	35
Italy ³⁹	220		30% <20 ms	66
Greece ⁴⁰	159		68% <20 ms	32
Worldwide survey ⁴¹	3445	20	22	58

From: Pennell D, Udelson J, Arai A et al. Cardiovascular function and treatment in β -thalassaemia major: a consensus statement from the American Heart Association. *Circulation* 2013;128:281-308.

Since 1999, there has been a marked improvement in survival in thalassaemia major in the UK. A study by Modell et al [10], in 2008, looking at survival and causes of death amongst patients on the UK Thalassaemia Register found that the main causes of death were anaemia (before 1980), infections, complications of bone marrow transplantation and cardiac disease due to iron overload. Between 1980 and 1999, there were 12.7 deaths from all causes per 1,000 patient years whereas, between 2000 and 2003, the death rate from all causes fell significantly to 4.3 per 1,000 patient years (-62%, $p < 0.05$). This was driven mainly by a reduction in the rate of deaths

² mg Fe/g dw liver = milligrams of iron per gram dry weight of liver

from iron overload which fell from 7.9 to 2.3 deaths per 1,000 patient years (-71%, $p < 0.05$). The most likely causes for the improved survival in thalassaemia major are thought to be the introduction of T2*-MRI to identify myocardial iron coupled with intensification of iron chelation treatment and other improvements in clinical care. The important role of cardiac T2*-MRI in identifying patients at risk of heart failure and arrhythmia from cardiac iron overload and reducing mortality is demonstrated by studies such as that by Kirk et al (2009)[11] and Chouliaris (2011)[12]. The Kirk study showed that T2*-MRI has a high predictive value for heart failure and arrhythmia in patients with thalassaemia major. The Chouliaris study showed that the addition of information from MRI to the management of more than 800 patients with thalassaemia major reduced the risk of cardiac death from 6.0 deaths/1000 patient-years to 3.9 deaths/1000 patient-years ($p = 0.22$).

2.2 Iron overload in sickle cell disease

Less is known about the incidence of iron overload in SCD. Patients with SCD may be relatively protected from iron-induced cardiac and endocrine organ damage compared with β -thalassaemia major patients [13]. In a study by Wood et al [14], 17 patients with SCD were compared with 19 patients with thalassaemia major matched for age, sex, transfusion duration, chelation therapy, and hepatic iron content. Cardiac iron overload, measured by T2-MRI, and cardiac dysfunction were significantly more prevalent in the thalassaemia group than the SCD group.

Transfusional iron overload is nevertheless a significant clinical issue in SCD. A recent review by Porter et al [15] cited one study in which iron overload was present in approximately one-third of 141 adult SCD patients at post mortem (mean age, 36 years), and 7% of deaths were considered to be related to iron overload [16]. In a second study, published in abstract only, of a cohort of 387 young adults in the USA, almost half (45% of 22 deaths) were related to iron overload [17]. These high levels of iron overload may reflect suboptimal management of patients with SCD at risk of iron overload. A third study by Meloni et al (2014)[18] suggests that cardiac iron overload occurs in only a small percentage of chronically transfused SCD patients and is only associated with exceptionally poor control of total body iron stores.

3 The measurement of iron overload using MRI

3.1 Technical basis for measurement of iron overload

As described by Wood [19], MRI operates like many other imaging modalities by transmitting a signal into the body after it has interacted with the microenvironment. With MRI, the transmitted signal is a microwave which excites water protons in the body to higher magnetic energy states. As the water protons relax back to an unexcited state, they emit microwaves that are received and interpreted by the scanner and which reflect the magnetic environment around the protons. In tissues which are not iron-overloaded, the magnetic environment is fairly homogeneous; signals received from different areas in the tissue remain coherent with one another and last for a long duration, giving bright images without much contrast. Conversely, iron deposits act like small magnets placed in a strong magnetic field; protons diffusing along different paths experience wildly different magnetic profiles, disrupting coherence among the protons and darkening the image more quickly.

MRI has the ability to 'refocus' the radio waves from the tissues at specific time intervals known as echo times. The longer the echo time, the more discordant the proton signals and the darker the image. Iron overloaded liver darkens more quickly with echo time. The MRI scanner can re-focus the returning signal either using a special radiofrequency pulse ('spin echo') or by using special small magnets known as gradients ('gradient echo'). The time constant for a spin echo (SE) is

known as T2 and for a gradient echo (GRE) is known as T2*. As tissue iron increases, the signal half lives shorten and both T2 and T2* become smaller.

Some investigators prefer to report rates of signal decay, R2 or R2*, which are simply the reciprocals of T2 and T2*. These distinctions are computational and not related to the imaging itself. R2 is equal to $1000/T2$ and R2* is equal to $1000/T2^*$. The factor of 1000 is used because T2 and T2* are reported in milliseconds whereas the units of R2 and R2* are Hertz³. The advantage of R2 and R2* values is that these are directly rather than indirectly proportional to iron.

MRI scanners need to be specifically set up for either R2 (equivalent to T2) or R2* (equivalent to T2*) methodology. Once proper images are acquired, images must be computer processed to generate the R2 or R2* values. Most sites have developed their own local expertise by contracting physicists or programmers to write the reconstruction algorithms. Other sites have used commercially available software, clinically validated for this application, to generate iron estimates; such software incorporates safeguards against incorrect handling and interpretation of the data, which can have clinical implications. Other sites use the services of commercial organisations (see measurement of liver iron below) to generate iron estimates.

3.2 Measurement of liver iron

A variety of MRI methods have been used to measure liver iron including R2-weighted spin-echo MRI (from here on referred to as R2-MRI or its reciprocal T2-MRI), with or without signal intensity ratios (SIRs) to adjacent tissues, and R2* gradient-echo MRI (from here on referred to as R2*-MRI or its reciprocal T2*-MRI), with or without SIR. More recently, other techniques have been introduced specifically for LIC determination. Of these, the R2 technique 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); a software application (FerriScan®) 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 FerriScan®, is designed to improve consistency in measurement and reporting across different centres [20].

3.3 Measurement of cardiac iron

The existing reference standard for measurement of cardiac iron is cardiac T2*-MRI. Gradient-echo T2*-MRI is the preferred technique for measurement of cardiac iron rather than a spin-echo T2-MRI sequence because of its greater sensitivity to iron deposition and lower sensitivity to motion, which is an important consideration in cardiac measurements. A multi-echo sequence (referred to as multi-echo gradient echo) is standard because this allows the acquisition of a single short-axis mid-ventricular slice at multiple echo times in a single breath hold. The most recent technical improvement in the T2* sequence has been the development of the black blood sequence⁴ although, at present, the white blood T2* sequence is more widely available across the UK.

³ One Hertz is equal to 1 cycle per second.

⁴ Cardiac MRI technique in which resulting images display very dark blood and substantially reduced image artifacts, enabling improved visualisation of cardiac anatomy.

4 Findings

We conducted a search of Medline, Embase and Medion Database for studies published in English from 2004 onwards. The search was limited to systematic reviews, trials, and comparative studies. Further details of the search strategy are provided in section 9 of this report.

4.1 Accuracy of MRI methods in diagnosing and/or monitoring iron overload

To assess the accuracy of different MRI methods in diagnosing and/or monitoring iron overload in patients with thalassaemia, sickle cell anaemia and/or rare transfusion-dependent anaemias, we identified studies involving a comparison between MRI measurement of iron overload and the relevant reference standard (liver biopsy for measurement of liver iron concentration; T2*-MRI for measurement of cardiac iron overload) in these patient groups.

Liver iron overload

We found nine individual studies comparing liver MRI with liver biopsy in patients with thalassaemia, sickle cell anaemia and/or rare transfusion-dependent anaemias. We selected five of these studies, by St Pierre (2005 and 2014) [21,22], Garbowski (2014) [23], McCarville (2010) [24], and Hankins (2009) [25], for inclusion in this review. Four of the studies, by Ooi (2004) [26], Wood (2005) [27], Alexopoulou (2006) [28], and Rose (2006) [29], were small (three involved less than 25 patients and one, by Ooi, involved 32 patients) and all had significant potential for bias in their methodology so were not considered further in this review.

Table 2 provides a summary of the methodology and results of the five individual studies included in this review.

Studies of R2*-MRI or T2*-MRI

Two studies, by McCarville [24] and Hankins [25], 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 the McCarville study, 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); in the Hankins study, none of the patients had liver iron concentration higher than 17.7 mg Fe/g dw liver. 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.

The Garbowski study [23] compared liver T2*-MRI (and its reciprocal R2*-MRI) with liver biopsy in 25 patients, in whom the most common diagnosis was β -thalassaemia major and liver iron concentration ranged from 1.7 to 42.3 mg Fe/g dw liver. The study had some methodological weaknesses in that it was small in size and the method of patient selection was unclear, although MRI observers were blinded to the biopsy results and to each others' findings. After log-transformation of both variables, statistical analysis showed high correlation between T2*-MRI and biopsy LIC (Pearson r -0.94).

Although all three studies investigated the level of agreement between the index test and reference test, none of them published information to enable estimation of the diagnostic accuracy of the MRI technique at pre-specified, clinically important LIC thresholds.

Studies of R2-MRI

Two studies by St Pierre [21, 22] 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. The 2014 study was much larger than the 2005 study, 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.

As shown in Table 2, the two studies by St Pierre both 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 St Pierre 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)[30]; 3.2 mg Fe/g dw liver (the suggested lower limit of the optimal range of LICs for chelation therapy in transfusional iron overload)[31]; 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)[31], 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)[31]. 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.

The larger and more methodologically sound St Pierre study in 2014 did not publish information to enable estimation of the diagnostic accuracy of the MRI technique at pre-specified LIC thresholds.

Table 2: Summary of studies comparing liver MRI with liver biopsy in determination of liver iron overload

Study	Population	Index test	Reference test	Results	Comments
St Pierre 2014	233 patients with β -thalassaemia receiving regular transfusions and chelation therapy.	Single spin echo (spin-density projection-assisted SDPA) liver R2-MRI (FerriScan®). 1.5Tesla (1.5T) ⁵ scanners of differing makes/models at five centres using standard protocol.	Liver biopsy - histological examination and quantitative LIC measurement via AAS ⁶ in single laboratory.	Biopsy LIC ranged from 0.7 to 50.1mg Fe/g dry weight (dw). ⁷ Upper and lower 95% limits of agreement between R2-MRI and biopsy LIC were 74% and -71% respectively, mean % difference 1.9 +/- SE ⁸ 2.4%. R2 calibration curve unaffected by differences in stage of liver fibrosis, grade of liver necroinflammation, patient age, use of chelation and type of scanner. No information given to allow estimation of sensitivity, specificity, PPV ⁹ , NPV ¹⁰ or LR ¹¹ .	Method of patient selection not clear. All patients had both R2 and liver biopsy. MRI data analysts blinded to biopsy LIC results. Mean timing of MRI scan after biopsy 15 +/- 38 days.
Garbowski 2014	25 patients with transfusional haemosiderosis (20 with β -thalassaemia major; 5 with different forms of anaemia); 31 healthy controls.	Multi-echo gradient echo liver T2*-MRI and R2*-MRI on single 1.5T scanner. Performed in triplicate by two independent observers using different region of interest (ROI) in liver.	Liver biopsy (LIC measured at single central laboratory). Two biopsies per patient/healthy control.	Biopsy LIC values ranged from 1.7 to 42.3 mg Fe/g dw liver (median 12.6). T2* (log-transformed) highly correlated with biopsy LIC variables ($r = -0.94$); same for R2* ($r = 0.94$). No information given to enable estimation of sensitivity, specificity, PPV, NPV or LR.	Small retrospective study. Method of patient selection not clear. All 25 patients had both T2*/R2*-MRI and liver biopsy; healthy volunteers had R2*-MRI and liver biopsy. MR observers blinded to biopsy results and to each other's findings.

⁵ MRI magnetic field strength⁶ Atomic absorption spectrometry⁷ mg Fe/g dw liver = milligrams of iron per gram dry weight of liver. Normal range 0.2 to 2.4 mg Fe/g dw liver⁸ Standard error⁹ Positive predictive value¹⁰ Negative predictive value¹¹ Likelihood ratio

					Median biopsy-to-scan window 78 days (range 2 to 228).
McCarville 2010	<p>41 patients (including 28 sickle cell, 5 β-thalassaemia, 5 other thalassaemias) with iron overload or >18 transfusions.</p> <p>Mean age 15.5 (range 7 to 35) years.</p>	<p>Multi-echo gradient echo R2*-MRI on single 1.5T scanner.</p> <p>Three independent reviewers.</p>	<p>Liver biopsy within 30 days after MRI.</p> <p>LIC quantification in single laboratory (via acid digestion, then plasma mass spectrometry).</p>	<p>Biopsy LIC ranged from 0.6 to 27.6 mg Fe/g dw liver (mean 10.3 mg Fe/g dw liver).</p> <p>Strong correlation between biopsy LIC and liver R2* (r 0.96 to 0.97, P<0.0001) for all three reviewers; correlation was strongest at lower LIC and R2* values and progressively decreased at higher values (especially >25 mg Fe/g dw liver).</p> <p>Range of R2* values and their standard errors were smaller with whole liver ROI than with small ROI.</p> <p>No information given to allow estimation of sensitivity, specificity, PPV, NPV or LR.</p>	<p>Method of patient selection not clear.</p> <p>Study participants did not include full spectrum of iron overload i.e. no patients with overload >28 mg Fe/g dw liver.</p> <p>All patients had biopsy within 30 days of MRI.</p> <p>MR reviewers blinded to biopsy LIC.</p>
Hankins 2009	<p>43 patients (including 32 sickle cell, 6 β-thalassaemia major) with iron overload (ferritin >1000 ng/ml) or >18 transfusions.</p> <p>Median age 14 years.</p>	<p>Multi-echo gradient echo R2*-MRI on single 1.5T scanner.</p>	<p>Liver biopsy.</p> <p>Two specimens – one for LIC quantification, the second for histology review by pathologist.</p>	<p>Average LIC 10.9 +/- 6.8 mg Fe/g dw liver.</p> <p>Mean R2* ranged from 394 +/- 234 to 412 +/- 239 Hz.</p> <p>Strong correlation observed between liver R2* and biopsy LIC (r = 0.96 to 0.98; p<0.001).</p> <p>Of 43 patients, 9 had no fibrosis; 19 had Grade I fibrosis; the rest had fibrosis grades 2 to 6.</p> <p>No information given to allow estimation of sensitivity, specificity, PPV, NPV or LR.</p>	<p>Method of patient selection not clear. Five patients had bone marrow failure; results not presented separately for each diagnostic group.</p> <p>Most patients young with low fibrosis and little chelation exposure.</p> <p>All patients had MRI within 30 days of biopsy.</p> <p>Pathologist blinded to clinical status and LIC. MRI reviewers blinded to clinical status and other reviewers' findings.</p>

<p>St Pierre 2005</p>	<p>105 patients including:</p> <p>9 with β-thalassemia on regular blood transfusions and chelation therapy (age range, 8-36 years);</p> <p>41 with β-thalassemia or haemoglobin E not on blood transfusions or chelation therapy (age range, 12-63 years);</p> <p>23 with hereditary haemochromatosis;</p> <p>32 with hepatitis and no iron overload.</p>	<p>Single spin echo R2-MRI using five 1.5T scanners of two different types.</p> <p>Reproducibility between scanners assessed in 10 people (3 healthy volunteers, 5 β-thalassemia major, 2 hereditary haemochromatosis) via 2 scans on 2 consecutive days.</p>	<p>Liver biopsy - quantitative LIC measured via AAS in 4 different laboratories.</p>	<p>Biopsy LIC ranged from 0.3 to 42.7 mg Fe/g dw liver.</p> <p>Biopsy LIC and liver R2-MRI were significantly highly correlated ($r = 0.98$, $P < 0.0001$).</p> <p>At LIC threshold of 1.8 mg Fe/g dw liver¹², sensitivity of R2-MRI for predicting biopsy LIC was 0.94 (95% CI 0.86 to 1.00), specificity 1.0 (95% CI 0.88 to 1.00), area under ROC¹³ plot 0.991 (SE¹⁴ 0.008).</p> <p>At LIC threshold of 3.2 mg Fe/g dw liver¹⁵, sensitivity was 0.94 (95% CI 0.85 to 0.98), specificity 1.0 (95% CI 0.91 to 1.00), area under ROC plot 0.988 (SE 0.010).</p> <p>At LIC threshold of 7.0mg Fe/g dw liver¹⁶, sensitivity was 0.89 (95% CI 0.79 to 0.95), specificity 0.96 (95% CI 0.86 to 0.99), area under ROC plot 0.991 (SE 0.009).</p> <p>At LIC threshold of 15.0 mg Fe/g dw liver¹⁷, sensitivity was 0.85 (95% CI 0.70 to 0.94), specificity 0.92 (95% CI 0.83 to 0.96), area under ROC plot 0.982 (SE 0.0016).</p>	<p>Patients selected were those about to undergo liver biopsy for assessment of iron overload or liver disease.</p> <p>MRI scans within 1 to 2 months of liver biopsy.</p> <p>No reported blinding of MRI reviewers.</p>
-----------------------	---	--	--	---	--

¹² Upper 95% limit of normal for LICs [30]

¹³ Receiver operator characteristic

¹⁴ Standard Error calculated using Hanley and McNeil method [32]

¹⁵ Suggested lower limit of the optimal range for LICs for chelation therapy in transfusional iron overload [31]

¹⁶ Suggested upper limit of the optimal range for LICs for transfusional iron overload and threshold for increased risk of iron-induced complications [31]

¹⁷ Threshold for greatly increased risk for cardiac disease and early death in patients with transfusional iron overload [31]

Systematic review by Sarigianni et al [33]

A systematic review (SR) and meta-analysis by Sarigianni et al on the accuracy of MRI in the diagnosis of liver iron overload was published online in June 2014, and appeared on PubMed after the date of our literature search. We have included it here because it represents a higher level evidence than that provided by the individual studies already described and is highly relevant to this review.

Table 3 summarises the methodology and findings of the Sarigianni SR which included 20 individual studies, published between 2001 and 2014, involving a total of 819 patients. All of the individual studies described earlier in this section were included in the SR, apart from that by Garbowski et al which was published later than the SR search date.

The SR was well conducted. For every included study, data was extracted to reconstruct 2 × 2 tables¹⁸ for each of three clinically relevant liver iron concentration (LIC) values and the corresponding MRI positivity thresholds. The selected LIC values were derived from Olivieri et al [31] (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). 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 SR 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.

¹⁸ The reviewers contacted authors of original studies for missing or unclear data. For studies, with no 2x2 table but for which raw data was available, they calculated MRI positivity thresholds based on a study-specific linear regression line.

Table 3: Summary of systematic review and meta-analysis by Sarigianni et al

Studies	Population	Index test	Reference test	Outcomes	Comments
20 studies (all either cohort or case control in design) Search date June 2013	819 patients with hereditary haemochromatosis, haemoglobinopathy or myelodysplastic syndrome (range n=8 to 233, median 26) Reported age range 3 to 79 (median 31) years 40% to 77% males	MRI using 1.5T scanners	Liver biopsy with chemical quantification of liver iron concentration Time interval between index and reference test, where reported, varied from <1 to 12 months.	For liver biopsy LIC threshold >7mg Fe/g dw liver (17 studies), MRI sensitivity ranged from 0.00 to 1.00 (median 0.94); specificity ranged from 0.50 to 1.00 (median 0.89). Substantial heterogeneity observed between studies, attributed to different MRI sequences and variable positivity thresholds. In sub-group analyses, both T2 and T2* MRI sequences had good diagnostic accuracy for identifying patients at risk for iron-induced complications or requiring titration of chelation therapy (>7 mg Fe/g dw liver). For T2-MRI, sensitivity 0.90 (95% CI 0.85 to 0.94), specificity 0.87 (0.76 to 0.93), NPV 0.83 (0.78 to 0.88), PPV 0.81 (0.77 to 0.86), NLR ¹⁹ 0.10 (0.07 to 0.14), PLR ²⁰ 8.85 (4.91 to 15.93), diagnostic OR 59 (22 to 158). For T2*-MRI, sensitivity 0.96 (95% CI 0.87 to 0.99), specificity 0.80 (0.53 to 0.94), NPV 0.88 (0.79 to 0.98), PPV 0.74 (0.66 to 0.83), NLR 0.05 (0.02 to 0.17), PLR 4.86 (1.74 to 13.58), diagnostic OR 92 (15 to 559). Results for other LIC thresholds (>2 or >15 mg Fe/g dw liver) were highly inconsistent and could not be pooled reliably.	All studies considered at high risk of bias. Many studies did not provide adequate details regarding method of patient selection and blinding of MRI assessors. Reference standard not used for all patients in 8 studies (n=232). Not all patients included in analysis in 9 studies (n=466). Most studies did not report 2 by 2 tables for diagnostic accuracy of MRI and, instead, presented correlation plots without explicit and pre-specified index test (MRI) positivity thresholds.

¹⁹ Negative likelihood ratio²⁰ Positive likelihood ratio

Cardiac iron overload

Five studies 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, by Kim (2010) [34], Cheung (2011) [35], and Song (2007) [36], each involved fewer than 15 patients and no control group, so were not considered further in this review. Two studies, by Feng (2013) [37] and He (2009) [38], each involved more than 100 patients and are summarised in Table 4.

Both the Feng and He studies 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 studies 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. Both studies 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. The Feng study also showed a strong correlation between cardiac T1-MRI and T2*-MRI for patients with myocardial iron.

Table 4: Summary of studies comparing MRI method with reference standard T2*-MRI in determination of cardiac iron overload

Study	Population	Index test	Reference test	Results	Comment
Feng 2013 International study: China, England, Germany	106 patients with thalassaemia major, all on regular iron chelation therapy. Aged 29 +/- 10 years.	Black-blood cardiac T2-MRI sequence and T1-MRI ²¹ sequence using single 1.5T scanner	Black-blood cardiac T2*-MRI using same 1.5T scanner as for T2 and T1 measurements	T2* values ranged from 4.2 to 41.7 ms (mean 22.3 +/-24.0 ms) corresponding to myocardial iron loading of 8 mg/g to 0.5 mg/g dw; T2 values ranged from 25.9 to 65.5 ms (mean 8.9 +/- 22.2 ms); T1 ranged from 474 to 1033 ms (mean 797 +/- 265 ms) and 474 to 804 ms in patients with abnormal T2*. Linear correlation between T2 and T2* (r =0.82, P = <0.05) and between T1 and T2* (r =0.83, P = <0.05) for patients (n=52) with myocardial iron overload but no such correlation for patients with normal myocardial iron.	Method of patient selection not clear. Almost half (48.1%) of the study population had myocardial iron loading (T2* < 20 ms). All patients studied had T1, T2 and T2*. No independent blinding of investigators to results from different MRI sequences.
He 2009 England	136 patients with thalassaemia, regularly transfused and on iron chelation therapy. Aged 27+/- 21 years.	Cardiac T2-MRI Measured via single 1.5T scanner	Black-blood cardiac T2*-MRI via 1.5T scanner (same as for T2 measurement)	T2* values ranged from 3.6 to 44.9 ms (median 15.9); T2 values ranged from 24.8 to 68.5 ms (median 44.2). Linear correlation between T2* and T2 (R ² = 0.89) for patients with iron overload (T2* ≤ 20 ms); no significant relationship between T2* and T2 for patients with no myocardial iron.	Method of patient selection not clear. All patients studied had both T2 and T2*. No independent blinding of investigators to results from different MRI sequences.

²¹ T1-MRI sequences involves short repetition time and short echo time; T2 sequence involves long repetition time and long echo time.

Trials in progress

A search was made on the clinicaltrials.gov website (in July 2014) for ongoing studies comparing MRI methods and the relevant reference standard in the measurement of liver or cardiac iron in patients with haemoglobinopathies or transfusion-dependent anaemias. No such studies were identified.

4.2 Safety

As reported by Bulfone et al in 2010 [39], since 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 [39].

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% [40].

The assessment of LIC by MRI is therefore likely to offer safety advantages when compared with liver biopsy.

4.3 Summary of section 4

Liver iron overload

Three of the five studies included in this review (by lead authors Hankins, McCarville and Garbowski) showed that liver T2*-MRI (or R2*) is correlated with liver biopsy iron concentration. Two of the studies (by lead authors McCarville and Hankins) involved small study populations in whom the predominant diagnosis was sickle cell disease and liver iron concentrations were less than 28 mg Fe/g dw liver; in one of these studies (McCarville), the correlation was weaker with increasing liver iron concentration. The third study by Garbowski in patients with a predominant diagnosis of β -thalassaemia and liver iron concentrations up to 42.3 mg Fe/g dw liver, showed high correlation between log-transformed variables of T2*-MRI (R2*) and biopsy liver iron concentration. None of the studies published information to enable assessment of diagnostic accuracy of the MRI techniques at pre-specified and clinically important LIC thresholds.

The two studies by St Pierre (in 2005 and 2014) showed that, in patients with β -thalassaemia, liver R2-MRI is correlated with liver biopsy iron across a wide range of liver iron concentrations (0.7mg to 50.1mg Fe/g dw liver in the 2014 study). The earlier St Pierre 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. The larger and more methodologically sound St Pierre study in 2014 did not publish information to enable estimation of the diagnostic accuracy of the MRI technique at pre-specified LIC thresholds.

A recent, well conducted systematic review of 20 individual studies found that sensitivity of MRI ranged from 0.00 to 1.00 (median 0.94) and specificity ranged from 0.50 to 1.00 (median 0.89) above an LIC threshold of greater than 7 mg Fe/g dw liver. Subgroup analyses of T2-MRI and T2*-MRI showed that both MRI sequences have good diagnostic accuracy for identifying patients at risk of iron-induced complications or requiring titration of chelation therapy (>7 mg Fe/g dw liver). However, both of these MRI sequences are likely to be more accurate in 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 reported that only two studies have 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

Both the Feng and He studies compared cardiac T2-MRI with T2*-MRI in patients with β -thalassaemia who were receiving regular transfusions and chelation therapy, and had a wide range of liver iron concentrations. Both studies 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. The Feng study also showed a strong correlation between cardiac T1-MRI and T2*-MRI for patients with myocardial iron.

Two studies were identified which compared cardiac T2-MRI and T2*-MRI in patients with β -thalassaemia. Both studies, which had some methodological weaknesses, showed strong correlation between cardiac T2-MRI and the existing reference standard for measuring myocardial iron, cardiac T2*-MRI.

In terms of patient safety, MRI is generally viewed as a safe imaging modality and different MRI techniques are unlikely to have differing safety profiles. 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. The assessment of LIC by MRI is therefore likely to offer safety advantages when compared with liver biopsy.

5 Cost and activity

The R2 technique FerriScan® is estimated to cost around £150 more per scan than other MRI techniques used in the investigation of iron overload (personal communication: CRG leads, September 2014).

No other information on costs or activity associated with MRI techniques used in the investigation of iron overload was available at the time of writing this report.

6 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*). 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.

7 Discussion and conclusions

1. For all patients, transfused or non-transfused, who have haemoglobinopathies or rare anaemias and who might have iron overload, what is the accuracy of currently available MRI methods in diagnosing and monitoring liver iron compared with liver biopsy?

A recent, well conducted systematic review and meta-analysis by Sarigianni et al investigated the diagnostic accuracy of MRI methods in identifying liver iron overload in patients with haemoglobinopathies, hereditary haemochromatosis, or myelodysplastic syndrome. The study included 20 individual studies, all of which were considered to be at high risk of bias. For every included study, data was extracted to calculate sensitivity and specificity for each of three clinically relevant liver iron concentration values and the corresponding MRI positivity thresholds.

MRI sensitivity ranged from 0.00 to 1.00 (median 0.94); specificity ranged from 0.50 to 1.00 (median 0.89). Subgroup analyses were possible for only two MRI sequences, T2-MRI and T2*-MRI. Both MRI sequences were found to have good diagnostic accuracy for identifying patients at risk of iron-induced complications or requiring titration of chelation therapy (LIC positivity threshold of greater than 7 mg Fe/g dw liver). For T2-MRI, sensitivity was 0.90 (95% CI 0.85 to 0.94), and specificity 0.87 (0.76 to 0.93); for T2*-MRI, sensitivity was 0.96 (95% CI 0.87 to 0.99), and specificity 0.80 (0.53 to 0.94). Prevalence was a significant predictor of sensitivity and specificity. Further analyses indicated that both of these MRI sequences are likely to be more accurate in 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 MRI sequences T2-MRI and T2*-MRI (and hence, their reciprocals R2-MRI and R2*-MRI) appear to have equivalent levels of diagnostic accuracy. However, as highlighted by Sarigianni et al, only two studies have investigated the diagnostic accuracy of liver R2-MRI (Ferriscan®) compared with liver biopsy LIC in patients with iron overload. Both of these studies were conducted by the same lead researcher who has declared interest in the commercial organisation (Resonance Health Ltd) to which Ferriscan® is registered. Further evidence may be needed to independently confirm the accuracy of this protocol before it is adopted more widely.

To conclude, 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.

2. For all patients, transfused or non-transfused, who have haemoglobinopathies or rare anaemias and who might have iron overload, what is the accuracy of MRI methods in diagnosing and monitoring cardiac iron compared with cardiac T2*-MRI?

Two studies were identified which compared cardiac T2-MRI and T2*-MRI in patients with β -thalassaemia. Both studies, which had some methodological weaknesses, showed strong correlation between cardiac T2-MRI and the existing reference standard for measuring myocardial iron, cardiac T2*-MRI.

In conclusion, this review found 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. Furthermore, evidence from studies such as that by Carpenter et al (2011)[41], show 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. This evidence supports the continued use of T2*-MRI in the measurement of cardiac iron overload in transfusion-dependent patients.

Terms of Use

This document has been produced by SPH for NHS England. It must not be distributed or accessed or used for commercial purposes without prior written permission from NHS England. The purpose of this document is to review and summarise published evidence relating to clinical interventions. The findings may be applicable to the development of commissioning policy, but commissioning policy development is undertaken by NHS commissioners taking into account a wide range of other factors. SPH is not responsible for the development of commissioning policy. Use of this document is subject to agreement that SPH is fully indemnified against any liability that may arise through use of the information within this document.

© Solutions for Public Health 2014

Solutions for Public Health owns on creation, the copyright and all other intellectual property rights in this document unless otherwise indicated. The copyright protected material may be reproduced free of charge in any format or medium subject to the necessary permission provided it is reproduced accurately and not used in a misleading context. If any of the copyright items produced are being copied to others, the source of the material must be identified and the copyright status acknowledged.

8 References

1. Pennell D, Udelson J, Arai A et al. Cardiovascular function and treatment in β -thalassaemia major: a consensus statement from the American Heart Association. *Circulation* 2013;128:281-308.
2. Wood JC. Impact of iron assessment by MRI. *Haematology* 2011: 443-50.
3. UK Thalassaemia Society. Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK. London, 2008.
4. McLeod C, Fleeman N, Kirkham J et al. Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation. *Health Technology Assessment* 2009;13(1).
5. Roberts-Harewood M. Inherited haemolytic anaemias. *Medicine* 2009;37(3):143-8.
6. <http://www.patient.co.uk/health/Sickle-Cell-Disease-and-Sickle-Cell-Anaemia.htm> (Last accessed 09 July 2014).
7. Porter J, Vichinsky E, Rose C et al. A phase II study with ICL 670, a once daily iron chelator, in patients with various transfusion-dependent anaemias and iron overload. *Blood* 2004;104:872a.
8. Cappellini MD, Cohen A, Piga A et al. A Phase III study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassaemia. *Blood* 2006;107:3455-62.
9. Anderson LJ, Holden S, Davis B et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. *Eur Heart J*. 2001;22:2171-9.
10. Modell B, Khan M, Darlison M et al. Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. *Journal of Cardiovascular Magnetic Resonance* 2008;10:42.
11. Kirk P, Roughton M, Porter JB et al. Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassaemia major. *Circulation* 2009;120:1961-8.
12. Chouliaras G1, Berdoukas V, Ladis V et al. Impact of magnetic resonance imaging on cardiac mortality in thalassaemia major. *J Magn Reson Imaging* 2011;34:56-9.
13. Raghupathy R, Manwani D, Little JA. Iron overload in sickle cell disease. *Adv Haematol*. 2010: Article ID 272940.
14. Wood J. C. Wood, J. M. Tyszka, S et al. Myocardial iron loading in transfusion-dependent thalassaemia and sickle cell disease. *Blood* 2004;103:1934-6.
15. Porter J, Garbowski M. Consequences and management of iron overload in sickle cell disease. *Haematology* 2013:447-56.
16. Darbari DS, Kple-Faget P, Kwagyan J et al.. Circumstances of death in adult sickle cell disease patients. *Am J Hematol*. 2006;81(11):858-863.
17. Aduloju S, Palmer S, Eckman J. Mortality in sickle cell patient transitioning from pediatric to adult program: 10 years Grady Comprehensive Sickle Cell Center Experience [abstract]. *Blood (ASH Annual Meeting Abstracts)* 2008;112(11):1426.
18. Meloni A, Puliyl M, Pepe A et al. Cardiac iron overload in sickle-cell disease. *Am J Hematol* 2014;89:678-83.
19. Wood JC. Diagnosis and management of transfusion iron overload: the role of imaging. *Am J Haematol*. 2007;82:1132-5.
20. St Pierre TG, Clark PR, Chua-Anusorn W. Measurement and mapping of liver iron concentrations using magnetic resonance imaging. *Ann N Y Acad Sci*. 2005;1054:379-85.
21. St. Pierre TG, Clark PR, Chua-anusorn W et al. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. *Blood* 2005;105:855-861.
22. St Pierre TG, El-Beshlawy A, Elalfy M et al. Multicenter validation of spin-density projection-assisted R2-MRI for the noninvasive measurement of liver iron concentration. *Magn Reson Med*. 2014;71:2215-23

23. Garbowski MW, Carpenter JP, Smith G et al. Biopsy-based calibration of T2* magnetic resonance for estimation of liver iron concentration and comparison with R2 Ferriscan. *J Cardiovasc Magn Reson*. 2014;16:40.
24. McCarville MB, Hillenbrand CM, Loeffler RB et al. Comparison of whole liver and small region-of-interest measurements of MRI liver R2* in children with iron overload. *Paediatr Radiol*. 2010;40:1360-7.
25. Hankins JS, McCarville MB, Loeffler RB et al. R2* magnetic resonance imaging of the liver in patients with iron overload. *Blood* 2009;113(20):4853-5.
26. Ooi GC, Khong PL, Chan GC et al. Magnetic resonance screening of iron status in transfusion-dependent beta-thalassaemia patients. *Br J Haematol*. 2004;124:385-90.
27. Wood JC, Enriquez C, Ghugre N et al. MRI R2 and R2* mapping accurately estimates hepatic iron concentration in transfusion-dependent thalassemia and sickle cell disease patients. *Blood* 2005;106:1460-5.
28. Alexopoulou E, Stripeli F, Baras P et al. R2 relaxometry with MRI for the quantification of tissue iron overload in beta-thalassaemic patients. *J Magn Reson Imaging* 2006;23:163-70.
29. Rose C, Vandevenne P, Bourgeois E et al. Liver iron content assessment by routine and simple magnetic resonance imaging procedure in highly transfused patients. *Eur J Haematol*. 2006;77:145-9.
30. Bassett ML, Halliday JW, Powell LW. Value of hepatic iron measurements in early hemochromatosis and determination of the critical iron level associated with fibrosis. *Hepatology* 1986; 6:24-29.
31. Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassaemia. *Blood* 1997;89:739-761.
32. Hanley JA, McNeil BJ. The meaning and use of the area under receiver operating characteristic curves derived from the same cases. *Radiology* 1982; 143:29-36.
33. Sarigianni M, Liakos A, Vlachaki E et al. Accuracy of magnetic resonance imaging in diagnosis of liver iron overload: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2014 Jun 30. [Epub ahead of print]
34. Kim D, Jensen JH, Wu EX et al. Rapid monitoring of iron-chelating therapy in thalassaemia major by a new cardiovascular MR measure: the reduced transverse relaxation rate. *NMR Biomed*. 2011;24:771-7.
35. Cheung JS, Au WY, Ha SY et al. Reduced transverse relaxation rate (RR2) for improved sensitivity in monitoring myocardial iron in thalassaemia. *J Magn Reson Imaging* 2011;33:1510-6.
36. Song R, Cohen AR, Song HK. Improved transverse relaxation rate measurement techniques for the assessment of hepatic and myocardial iron content. *J Magn Reson Imaging* 2007;26:208-14
37. Feng Y, He T, Carpenter JP et al. In vivo comparison of myocardial T1 with T2 and T2* in thalassaemia major. *J Magn Reson Imaging* 2013;38:588-93.
38. He T, Smith GC, Gatehouse PD et al. On using T2 to assess extrinsic magnetic field inhomogeneity effects on T2* measurements in myocardial siderosis in thalassaemia. *Magn Reson Med*. 2009;61:501-6.
39. Bulfone L, Younie S, Murphy B. Assessment of liver iron by R2-MRI data analysis. MSAC Application 1131, Assessment Report. Commonwealth of Australia, Canberra, ACT, 2010.
40. Angelucci E, Baronciani D, Lucarelli G, et al. Needle liver biopsy in thalassaemia: analyses of diagnostic accuracy and safety in 1184 consecutive biopsies. *Br J Haematol*. 1995;89(4):757-61.
41. Carpenter J-P, He T, Kirk P et al. On T2* magnetic resonance and cardiac iron. *Circulation* 2011;123:1519-28.

9 Search Strategy

Search date July 2014.

Inclusion criteria for identification of studies

Population	Diagnostic intervention	Comparator	Outcome measures	Studies
Transfused patients with: a) thalassaemia major, thalassaemia intermedia b) sickle cell anaemia c) rare transfusion dependent anaemias such as diamond Blackfen and sideroblastic anaemias Non-transfused patients with thalassaemia intermedia	MRI methods for assessing liver iron and/or cardiac iron concentration/ overload i.e. Relaxometry: R2-MRI (FerriScan®), T2, R2*, T2* Signal intensity ratio(SIR)/Rennes SIR	Liver biopsy (for studies of liver iron overload) Cardiac T2*-MRI (for studies of cardiac iron overload)	Accuracy: Sensitivity Specificity Positive predictive value (PPV) Negative predictive value (NPV) Likelihood ratio (LR) Precision Reproducibility	Meta-analyses Systematic reviews RCTs Other controlled studies Any other clinical study

Search strategy:

1. exp Thalassemia/
2. anemia, hemolytic, congenital/ or exp anemia, sickle cell/
3. Anemia, Sideroblastic/
4. exp Anemia, Hypoplastic, Congenital/
5. Blood Transfusion/ and exp Anemia/
6. thalass?emi*.ti,ab.
7. ((sickle cell or diamond blackfan or sideroblast) adj3 an?emi*).ti,ab.
8. (transfus* adj5 an?emi*).ti,ab.
9. (transfusion dependen* and an?emi*).ti,ab.
10. Hemochromatosis/
11. h?emochromatosi*.ti,ab.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. liver/ and (iron/ or iron overload/)
14. ((hepatic or liver or hepato*) adj3 iron).ti,ab.
15. ((hepatic or liver or hepato*) and (iron overload or iron concentration)).ti,ab.
16. (myocardium/ or Heart/) and (iron/ or iron overload/)
17. ((heart or cardi* or myocardi*) adj3 iron).ti,ab.
18. ((heart or cardi* or myocardi*) and (iron overload or iron concentration)).ti,ab.
19. 13 or 14 or 15 or 16 or 17 or 18
20. exp Magnetic Resonance Imaging/
21. relaxometr*.ti,ab.
22. (mri or magnetic resonance imag*).ti,ab.
23. (r2* or t2*).ti,ab.
24. (signal intensity ratio* or (sir adj3 rennes)).ti,ab.
25. 20 or 21 or 22 or 23 or 24
26. 12 and 19 and 25

27. exp "Reproducibility of Results"/
28. exp "Sensitivity and Specificity"/
29. (sensitiv* or specific* or precision or predict* or ppv or npv or accura* or reproducib* or (repeat* adj2 (test* or measure*))) or repeatab* or correlat* or calibrat*).ti,ab.
30. (diagnos* or determinat* or measur*).ti.
31. 27 or 28 or 29 or 30
32. 26 and 31
33. Iron Overload/di [Diagnosis]
34. 12 and 25 and 33
35. ferriscan*.ti,ab.
36. 32 or 34 or 35
37. limit 36 to english language

For public consultation

For public consultation