EAG PROTOCOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

MRI-based technologies for the assessment of patients with non-alcoholic fatty liver disease [DAP59] – Protocol

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: MRI-based technologies for the assessment of patients with non-alcoholic fatty liver disease [DAP59] – Protocol

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LIST OF ABBREVIATIONS

ARFI	Acoustic radiation force impulse
BMI	Body mass index
BSG	British Society of Gastroenterology
CCG	Clinical Commissioning Group
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost effectiveness analysis
CENTRAL	Cochrane Central Database of Controlled Trials
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CRN	Clinical Research Network
DARE	Database of Abstracts of Reviews of Effects
DTA	Diagnostic test accuracy
ELF	Enhanced liver fibrosis
FIB-4	Fibrosis-4 index
HTA	Health technology assessment
EAG	External Assessment Group
MRE	Magnetic resonance elastography
MRI	Magnetic resonance imaging
MRR	Mortality rate ratio
MRS	Magnetic resonance spectroscopy
NAFLD	Non-alcoholic fatty liver disease
NAS	NAFLD activity score
NASH	Non-alcoholic steatohepatitis
NFS	NAFLD fibrosis score
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NG	NICE guideline
PDFF	Proton density fat fraction
QALY	Quality adjusted life year
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomised controlled trial
ROC	Receiver operating characteristic
TE	Transient elastography

1 PLAIN ENGLISH SUMMARY

Non-alcoholic fatty liver disease (NAFLD) includes a range of conditions that are caused by a build-up of fat in the liver and have not been caused by alcohol consumption. This build-up of fat can cause inflammation and persistent inflammation can cause scar tissue to develop. This scarring is called fibrosis. Severe fibrosis can cause permanent liver damage (cirrhosis), which can lead to liver failure and liver cancer. Patients with NAFLD undergo tests to identify whether they have fibrosis. Tests are not always accurate and multiple tests can give conflicting results. Some of the tests currently used in the NHS to detect fibrosis may not be suitable for patients who are obese or who have a very high body mass index.

It is estimated that between one in three and one in five people in the UK have early stages of NAFLD. Risk factors for NAFLD include type 2 diabetes, high blood pressure or high cholesterol, and being overweight or obese. Current guidelines recommend using the Fibrosis-4 (FIB-4) test, the NAFLD fibrosis score (NFS) test or the enhanced liver fibrosis (ELF) test to assess level of liver fibrosis. If test results are unclear further tests are needed and these include transient elastography (TE), acoustic radiation force impulse (ARFI) and the ELF test (if not previously carried out). In current NHS practice, a liver biopsy may be offered to patients whose test results are inconclusive or conflicting or for whom the use of TE or ARFI is not suitable.

LiverMultiScan is imaging software that is used alongside magnetic resonance imaging (MRI). It provides quantitative analysis of liver fat content, liver iron concentration and fibro-inflammation. LiverMultiScan protocols can be built into existing abdominal MRI protocols.

Magnetic resonance elastography (MRE) is used in some NHS centres to assess liver fibrosis; however, MRE requires more equipment than just an MRI scanner.

This project will explore whether LiverMultiScan and MRE can be used to assess patients with NAFLD, and will consider whether use of these technologies will offer good value for money to the NHS.

2 DECISION PROBLEM

2.1 Purpose of the assessment

NAFLD is an umbrella term for a range of conditions caused by a build-up of fat in the liver that has not been caused by alcohol consumption.[1] NAFLD covers a spectrum of histological lesions ranging from steatosis to a complex pattern that associates hepatocyte injury, inflammation and fibrosis.[2] Liver biopsy is the only diagnostic procedure that can reliably assess these various patterns and their association.[2] Biopsy results are essential to determine the treatment strategy and stratify prognostic risk for patients with NAFLD.[3] However, liver biopsy is an invasive procedure that is associated with well-recognised complications, including hospitalisation (1 to 3% of patients, most commonly because of pain or hypotension) and death (1 in 10,000 to 1 in 12,000).[4]

The purpose of this assessment is to explore whether two non-invasive magnetic resonance imaging (MRI) based technologies, specifically LiverMultiScan and magnetic resonance elastography (MRE), can be used to assess NAFLD and whether use of these technologies represents a cost effective use of NHS resources compared to a diagnostic pathway that does not include them.

2.2 Target condition

Risk factors for NAFLD include type 2 diabetes, high blood pressure or high cholesterol, underactive thyroid, smoking and being overweight or obese.[5] It is estimated that between one in three[1] and one in five people[6] in the UK have early stages of NAFLD. The prevalence of NAFLD increases with age and is most prevalent in men aged 40 to 65 years.[7] However, the prevalence of NAFLD is increasing in younger people due to rising levels of obesity among children (aged 1 to under 16 years) and young people (aged 16 to under 18 years).[8] Studies have reported that 34% to 38% of children with obesity show histological evidence of NAFLD.[9]

The four main stages of NAFLD are:[6]

1. simple fatty liver (steatosis) - a largely harmless build-up of fat in liver cells
2. non-alcoholic steatohepatitis (NASH) - the build-up of fat in the liver leads to inflammation. Approximately 20% of patients with NAFLD develop NASH
3. fibrosis - persistent inflammation develops in response to the build-up of fat and causes scar tissue formation in the liver and blood vessels. Approximately 25 to 40% of patients with NASH develop liver fibrosis[10]
4. cirrhosis - chronic inflammation in the liver produces severe and irreversible scarring causing liver damage. Approximately 20% to 30% of patients with NASH develop cirrhosis.[10] Cirrhosis can lead to liver failure and liver cancer.[11]

It is estimated that 3.3 million people in the UK have NASH[6] and that approximately 80% of these cases are undiagnosed because early-stage NASH is usually asymptomatic.[12,13] It is widely accepted that liver fibrosis develops as a result of liver damage that is secondary to NASH.[14] Compared to patients with NAFLD with no fibrosis (F0), the risk of liver-related mortality in patients with NAFLD with fibrosis increases exponentially with each stage of fibrosis (F1, mortality rate ratio [MRR]=1.41, 95% confidence intervals [CI] 0.17 to 11.95); F2, MRR=9.57, 95% CI 1.67-54.93; F3, MRR=16.69, 95% CI 2.92-95.36; and F4, MRR=42.30, 95% CI 3.51-510.34).[15]

NASH can progress to compensated cirrhosis (asymptomatic) and decompensated cirrhosis (symptomatic).[16] Approximately 1% of patients with NASH will develop hepatocellular carcinoma and a smaller percentage (0.04%) may require liver transplantation.[16]

The NASH Clinical Research Network (CRN) system uses the NAFLD Activity Score (NAS) to assess the histological stage of NAFLD from liver biopsy (Table 1).[17] The NAS is the unweighted sum of steatosis, lobular inflammation and hepatocellular ballooning scores. A NAS score ≥5 indicates a diagnosis of NASH.[17]

Table 1 NASH Clinical Research Network histological scoring system

NAFLD activity score (NAS)					
Steatosis		**Hepatocyte ballooning**		**Lobular inflammation (foci per 200x field)**	
0	<5%	0	None	0	None
1	5% to 33%	1	Few	1	<2
2	34% to 66%	2	Many	2	2 to 4
3	>66%	-	-	3	>4

NAFLD=non-alcoholic fatty liver disease; NAS-NAFLD Activity Score
Source: Kleiner et al 2005[17]

2.3 Current NHS diagnostic practice

The National Institute for Health and Care Excellence (NICE) guideline[8] (Non-alcoholic fatty liver disease: assessment and management, NG49) includes a summary of current best practice for the diagnosis and management of NAFLD.

In NG49,[8] it is recommended that clinicians should:

- suspect NAFLD in patients with type 2 diabetes or metabolic syndrome
- take an alcohol-related history from patients presenting with symptoms of NAFLD to rule out alcohol-related liver disease
- not use routine liver blood tests to rule out NAFLD.

For adults, NAFLD is most often suspected following abnormal liver function test results in the primary care setting,[18] or following an incidental ultrasound finding.[8,19]

NG49[8] includes a review of the diagnostic test accuracy evidence. Results from this review were used to identify the most accurate assessment tool for diagnosing NAFLD in adults, young people and children, and for identifying the severity or stage of NAFLD. The recommendations are as follows:

- offer testing for advanced liver fibrosis to patients with NAFLD and consider using the enhanced liver fibrosis (ELF) test
- patients with NAFLD and an ELF score ≥10.51 should be diagnosed with advanced liver fibrosis
- patients with NAFLD and an ELF score <10.51 are unlikely to have advanced liver fibrosis and should be reassessed regularly (adults every 3 years, and children and young people annually)
- offer a liver ultrasound to test children and young people for NAFLD if they have type 2 diabetes or metabolic syndrome and do not misuse alcohol. Children and young people are diagnosed with NAFLD if a fatty liver is detected on ultrasound. If the ultrasound is normal, then offer to retest with liver ultrasound for NAFLD every 3 years.

NG49[8] does not include a recommendation for any diagnostic test for the diagnosis of NASH, but does include a recommendation for research of non-invasive tests that accurately diagnose NASH in patients with NAFLD.

The British Society of Gastroenterology (BSG) national guidelines[20] and the Lancet Commission into liver disease in the UK[21] recommendations are that the Fibrosis-4 (FIB-4) test and the NAFLD fibrosis score (NFS) test should be used as first-line testing to assess the stage of fibrosis.

In the BSG national guidelines,[20] the recommendations are as follows:

- a FIB-4 score ≤1.30 or a NFS ≤-1.455 demonstrates that patients have low risk of advanced fibrosis
- patients with low risk of advanced fibrosis can be managed in primary care and advised on lifestyle modifications
- patients with an indeterminate FIB-4 score (1.3 to 3.25) or NFS (-1.455 to 0.675) should undergo second-line testing using the ELF test, transient elastography (TE) or acoustic radiation force impulse (ARFI)
- patients with FIB-4 score >3.25 or NFS >0.675 should be considered to have high risk of advanced fibrosis and should be referred to a specialist clinic irrespective of second-line tests.

In the British Medical Journal (BMJ),[22] the recommendations are as follows:

- ultrasound should be used as first-line testing to diagnose hepatic steatosis and to exclude other liver pathology
- ELF and TE should be used to assess liver fibrosis for patients with confirmed hepatic steatosis
- patients with liver fibrosis should be referred to hepatology.

The tests used to diagnose advanced liver fibrosis vary by centre, depending on availability.[23] In NG49,[8] there is a list of alternative diagnostic tools that have been used in NHS clinical practice to diagnose and assess advanced fibrosis and cirrhosis. These tools include TE, ARFI, MRI, MRI proton density fat fraction (PDFF), magnetic resonance spectroscopy (MRS), magnetic resonance elastography (MRE), shear wave elastography and liver biopsy. The use of liver biopsy in current NHS diagnostic practice is described in Section 2.9.1.

Findings from a cross-sectional survey[23] of liver disease management, conducted from June to October 2020 indicated that only 25% (40/159) of UK Clinical Commissioning Groups (CCGs) used TE and only 16% (26/159) used the ELF test. Approximately two-fifths of UK CCGs (44%, 70/159) followed the BSG national guidelines recommendations[20] and used FIB-4 and NFS to assess liver fibrosis.

Figure 1 presents an overview of the current diagnostic pathway for the assessment of fibrosis in the NHS based on guidelines[7,8,20,22] and expert advice to NICE.

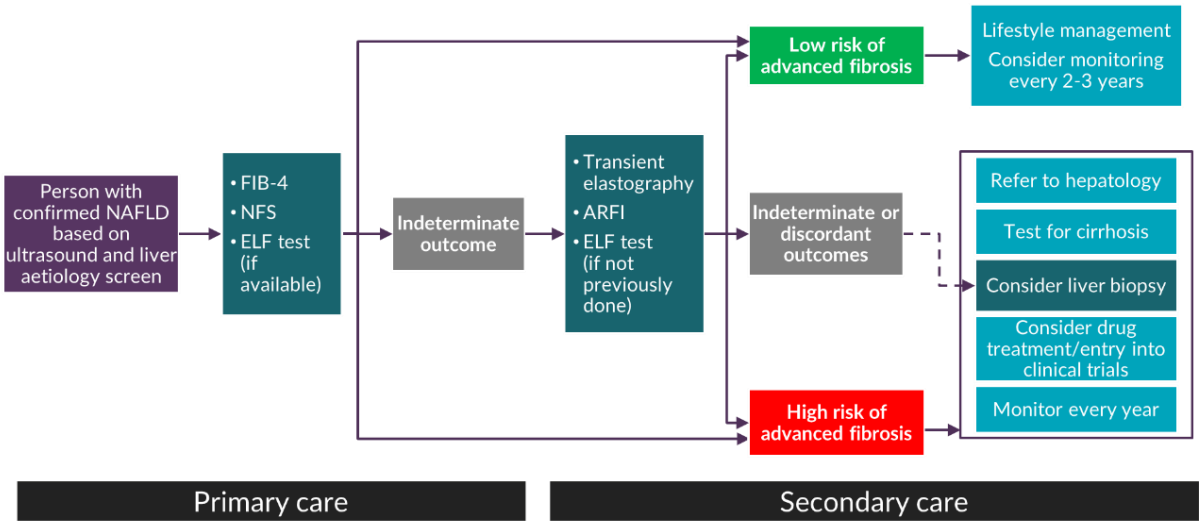

Figure 1 Overview of current diagnostic pathway for assessment of fibrosis in the NHS, based on guidelines and expert advice

ARFI=acoustic radiation force impulse; ELF=enhanced liver fibrosis; FIB-4=fibrosis-4; MRI=magnetic resonance imaging; NALFD=non-alcoholic fatty liver disease; NFS=NAFLD fibrosis score
Source: Final scope[24] issued by NICE

2.4 Treatment options

NG49[8] recommendations for lifestyle modifications for patients diagnosed with NAFLD are as follows:

- offer advice on physical activity and diet to patients with NAFLD who are overweight or obese and explain that exercise may reduce liver fat content
- consider the lifestyle interventions detailed in NICE's obesity guideline[25] for patients with NAFLD, regardless of their body mass index (BMI)

- explain the importance of adhering to the national recommended limits for alcohol consumption.

NG49[8] pharmacological therapy recommendations are as follows:

- pharmacological therapy may be considered in secondary or tertiary care settings only
- consider pioglitazone or vitamin E for adults with advanced liver fibrosis, whether they have diabetes or not
- consider vitamin E for children with advanced liver fibrosis, whether they have diabetes or not (only in tertiary care settings)
- consider vitamin E for young people with advanced liver fibrosis, whether they have diabetes or not
- offer to retest patients with advanced liver fibrosis 2 years after they start a new pharmacological therapy to assess whether treatment is effective
- consider using the ELF test to assess whether pharmacological therapy is effective
- if an adult's ELF test score has risen, stop either vitamin E or pioglitazone and consider switching to the other pharmacological therapy
- if a child or young person's ELF test score has risen, stop vitamin E.

Although pioglitazone or vitamin E may be offered to patients with advanced liver fibrosis,[8] clinical advice to NICE[24] is that this may not be done in NHS practice. There are currently no pharmacological treatments licensed specifically for the treatment of NAFLD, although novel therapies are in clinical development.[26] Patients with advanced fibrosis may be considered for entry into clinical trials.

2.5 Population

In line with the final scope[24] issued by NICE, the population of interest is patients with NAFLD for whom advanced fibrosis or cirrhosis has not been diagnosed. This population includes:

- patients who have indeterminate results from fibrosis testing
- patients for whom TE or ARFI is unsuitable
- patients who have discordant results from fibrosis testing.

If data permit, additional subgroup analyses will be considered (for example, based on prior tests for fibrosis, children or young people).

2.5.1 Patients who have indeterminate results from fibrosis testing

Results from TE, ARFI and ELF tests may indicate that some level of fibrosis is present but may not be able to confirm the presence of advanced fibrosis (F3).

In the BSG guidance,[20] a TE score between 7.9kPa and 9.6kPa indicates an intermediate risk of fibrosis and represents an indeterminate result. In the BSG guidance[20] it is recommended that clinicians should consider liver biopsy for patients with a TE score between 7.9kPa and

9.6kPa (indeterminate result), and for patients with a TE score >9.6kPa (high risk of fibrosis). In the NICE guideline[27] (Hepatitis B [chronic]: diagnosis and management, CG165), it is recommended that the degree of fibrosis cannot be accurately predicted in adults with a TE score between 6kPa and 10kPa and that in these circumstances some patients may choose to have a liver biopsy to confirm the extent of liver disease.

Clinical advice to NICE[24] is that indeterminate results are also possible from the ELF test and from ARFI, although the exact values for an indeterminate ARFI result depend on the device manufacturer. Indeterminate results from the ELF test are considered to range between 7.8 and 10.5,[22] or 7.7 and 9.7.[28]

In current NHS practice, a biopsy may be considered for patients with indeterminate results from fibrosis testing. MRI-based testing could be used as an additional, non-invasive, diagnostic test to help clinicians assess the need for a liver biopsy.

2.5.2 Patients for whom TE or ARFI is unsuitable

TE and ARFI may not be suitable tests for people with obesity, or those with a very high BMI, or those with ascites.[29] The tests may fail, or the clinicians may decide not to refer patients for these tests because they are likely to fail.

Liver biopsy may be considered for this subgroup of patients to determine the stage of fibrosis and to diagnose cirrhosis. MRI-based testing could be used as an additional, non-invasive, diagnostic test to help assess the need for a liver biopsy.

2.5.3 Patients who have discordant results from fibrosis testing

Patients with NAFLD may undergo multiple tests to confirm the presence of advanced fibrosis. If the results from these tests are discordant, then liver biopsy should be considered.[30] MRI-based testing could be used as an additional, non-invasive, diagnostic test to help assess the need for a liver biopsy.

2.6 Interventions / index tests

2.6.1 LiverMultiScan

LiverMultiScan (Perspectum Ltd) is a multiparametric MRI-based imaging software that provides quantitative analysis of liver fat content, liver iron concentration and fibro-inflammation from non-contrast MRI images. LiverMultiScan software enables assessment of liver fat content from MRI PDFF, liver iron concentration from T2* mappings and fibro-inflammation from T1 mappings. The T1 analyses for fibro-inflammation are adjusted for iron level to remove artefacts and increase accuracy.[31]

LiverMultiScan protocols can be integrated into existing abdominal MRI protocols on Siemens, Philips or GE Healthcare scanners.[24] LiverMultiScan typically requires a 15 minute scan acquisition time but does not require any contrast agent or additional hardware beyond the MRI scanner.[24] Training on how to use the LiverMultiScan protocol takes approximately 3 hours.[24] Specialist technical support is provided by the manufacturer as part of the licence. The imaging data from the MRI scan are sent to Perspectum Diagnostics via an Amazon hosted cloud service and are analysed by Perspectum trained operators.[32] The quantitative analysis is returned to clinicians in report format.[32]

2.6.2 Magnetic resonance elastography

MRE is a non-invasive MRI-based technique that uses a mechanical driver to generate shear waves across the liver during an MRI scan.[33] An MRI sequence with motion-encoding gradients measures the propagation of the shear waves across the liver to produce an image (elastogram) showing the distribution of liver stiffness.[33] MRE requires additional hardware to an MRI scanner, including an active acoustic driver, a passive pneumatic driver and a connector.[34] MRE can be used alongside standardised MRI PDFF and iron-assessment packages offered by scanner manufacturers to assess fat and iron.[35]

The MRE acquisition is performed during breath-holding and takes 12 to 15 seconds, which is typically repeated four times.[24] The total acquisition time can last approximately one minute.[24] Inadequate breath holding can produce image artefacts.[34]

The NICE guidelines (NG49[8] and NG50[36]) do not consider the use of MRE for diagnosing NAFLD or liver fibrosis or cirrhosis. However, MRE is used in some NHS centres where it is available when other diagnostic tests have returned indeterminate results. MRE is primarily used as a research tool.

2.7 Place of the intervention in the diagnostic pathway

The proposed positioning of MRI-based technologies is as an additional, non-invasive diagnostic test for further investigation in patients with NAFLD who have indeterminate results from fibrosis testing, for whom TE or ARFI is unsuitable or who have discordant results from fibrosis testing at this stage in the diagnostic pathway. At this stage, patients may currently be referred for liver biopsy. However, patients who are contraindicated, who do not wish to proceed with liver biopsy, or who are being treated at centres without access to these services may not undergo any further investigation. Results from MRI assessment could help make decisions about whether a liver biopsy is needed and about the extent of future monitoring. Results from MRI assessment may also allow targeted offering of lifestyle interventions or

improve uptake and compliance with these interventions to reduce the likelihood of progression to more severe NAFLD.

2.8 Comparator

In NHS current practice, the populations specified in the final scope[24] issued by NICE would not undergo any further investigation prior to deciding whether a biopsy should be done. Clinical experts to NICE commented that, in these populations, the probability of having a biopsy is based on clinical suspicion of advanced fibrosis or cirrhosis (for example, characteristics such as age, weight and comorbidities).[24]

2.9 Reference standard

To assess diagnostic test accuracy, the index tests (i.e., LiverMultiScan and MRE) will be compared to the results of a reference standard (i.e., liver biopsy). The reference standard is used to verify the presence or absence of the target condition. The reference standard for this assessment is liver biopsy performed and interpreted by a trained healthcare professional.

2.9.1 Liver biopsy

Liver biopsy, an invasive method, is considered the gold standard for staging liver fibrosis, inflammation and steatosis, and for diagnosing NASH.[8] During liver biopsy, a small sample of tissue is percutaneously or transvenously removed from the liver using a needle.[37] However, liver biopsies are associated with inter- and intra-observer variability and sampling error.[38,39] Liver biopsies are expensive because they require outpatient care, specialists (a gastroenterologist, hepatologist or radiologist) to obtain the biopsy and pathologists to examine and report the biopsy results.[8] Liver biopsies can be painful and are associated with a high risk of complications, including bleeding (10%) and major bleeding (<2%).[37]

In NG50,[36] it is recommended that clinicians should only consider a liver biopsy to diagnose cirrhosis in patients for whom TE is not suitable. In NG49,[8] it is stated that a liver biopsy should not be used to diagnose NAFLD or for monitoring disease progression, and that biopsies should be avoided in children and young people unless there is an unclear diagnosis or concern about rapid disease progression.

Clinical advice to NICE is that in some NHS centres liver biopsy is carried out in a large proportion of patients with significant or advanced fibrosis to either confirm diagnosis or to obtain a diagnosis to allow entry into clinical trials.

3 METHODS FOR ASSESSING DIAGNOSTIC TEST ACCURACY AND CLINICAL IMPACT

A single systematic literature review will be conducted to evaluate (1) the diagnostic accuracy of MRI-based technologies for the assessment of fibrosis, inflammation and steatosis in patients with NAFLD, using liver biopsy as the reference standard, and (2) the clinical impact of MRI-based technologies compared to no further testing. The methods for the systematic review will follow the general principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for conducting reviews in health care,[40] NICE's Diagnostics Assessment Programme manual[41] and the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (DTA).[42]

3.1 Search strategy

A single search strategy will be used to identify studies that address the review questions. The search strategy will be designed to focus on the index tests (i.e., LiverMultiScan and MRE) and target population (i.e., patients with NAFLD). No study design filters will be applied and all electronic databases will be searched from inception until the date of the search. The reference lists of relevant systematic reviews and eligible studies will be hand-searched to identify further potentially relevant studies. Data submitted by the companies/sponsors will be considered (see Section 5.1 for further details). The following databases will be searched for relevant studies:

- MEDLINE (via Ovid)
- MEDLINE Epub Ahead of Print and MEDLINE In-Process & Other Non-Indexed Citations (via Ovid)
- Embase (via Ovid)
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Central Database of Controlled Trials (CENTRAL)
- Database of Abstracts of Reviews of Effects (DARE) (via Centre for Reviews and Dissemination)
- Health Technology Assessment Database (HTA) (via International HTA Database).

Details of the draft MEDLINE search strategy are provided in Appendix 1. The MEDLINE search will be adapted to enable similar searching of the other relevant electronic databases. Records will be exported to EndNote X9, where duplicates will be systematically identified and removed.

3.2 Eligibility criteria

The eligibility criteria for inclusion of studies assessing the DTA or clinical impact of MRI-based technologies for the assessment of patients with NAFLD are presented in Table 2.

Table 2 Review eligibility criteria

Population	Patients with NAFLD for whom advanced fibrosis or cirrhosis has not been diagnosed: • Who have indeterminate results from fibrosis testing • For whom TE or ARFI is unsuitable • Who have discordant results from fibrosis testing If data permit, additional subgroup analyses will be considered (for example, based on prior tests for fibrosis, children or young people)	
Setting	Secondary and tertiary care	
Interventions	MRI-based technologies, i.e., LiverMultiScan and MRE	
	Diagnostic test accuracy	**Clinical impact**
Comparator	LiverMultiScan compared to MRE, or no comparator	No further testing
Reference standard	Liver biopsy performed and interpreted by a trained healthcare professional	Not applicable
Outcomes	Test accuracy for: • fibrosis • inflammation • steatosis	Intermediate outcomes • Impact of test result on clinical decision making (such as whether a biopsy is done, frequency of subsequent monitoring, lifestyle advice or intervention offered) • Prognostic ability (for example, to predict progression of fibrosis or clinical outcomes) • Number of liver biopsies • Uptake and maintenance of lifestyle modifications • Time to receive test results • Time to diagnosis • Test failure rate • Reduction or remission of liver fibrosis or fibro inflammation • Reduction or remission of liver fat
		Clinical outcomes • Mortality • Morbidity (can be liver-related and non-liver related, and including from complications related to liver biopsy)
		Patient-reported outcomes • Health-related quality of life • Acceptability of different testing modalities
Study design	Diagnostic cross-sectional and case-control studies	RCTs, cross-sectional, case-control/cohort studies & uncontrolled single arm studies

ARFI=acoustic radiation force impulse; MRE=magnetic resonance elastography; MRI=magnetic resonance imaging; NAFLD=non-alcoholic fatty liver disease; RCT=randomised controlled trial; TE=transient elastography

Studies that do not present original data (i.e., reviews, editorials and opinion papers), case reports and non-English language studies will be excluded from the review. Abstracts and manufacturer data will only be included if they provide numerical data and sufficient methodological detail to enable assessment of study quality/risk of bias. Further, only outcome data that have not been reported in peer-reviewed full-text papers will be extracted from abstracts and manufacturer reports.

3.3 Study selection

The citations identified will be imported into a review management system (Covidence) and will be assessed for inclusion in the review using a two-stage process. First, two reviewers will independently screen all the titles and abstracts of publications identified by the electronic searches to distinguish the potentially relevant studies to be retrieved. Second, full-text copies of these studies will be obtained and assessed independently by two reviewers for inclusion using the eligibility criteria outlined in Table 2. Any disagreements will be resolved through discussion at each stage and, if necessary, in consultation with a third reviewer.

3.4 Data extraction

A data extraction form will be designed, piloted and finalised to facilitate standardised data extraction. Data on study and patient characteristics and results will be extracted by one reviewer and independently checked by a second reviewer. Any disagreements will be resolved through discussion and, if necessary, in consultation with a third reviewer. If time permits, the manufacturers of the index tests and the corresponding authors of eligible studies will be contacted and asked to provide missing data or clarify data presented. The EAG may also request individual participant data from manufacturers of the index tests and the corresponding authors of eligible studies to allow analysis of specific populations as outlined in Table 2, and the subgroups listed in Section **Error! Reference source not found.**.

3.5 Quality assessment

The methodological quality of DTA studies will be assessed using the QUality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool[43] tailored to the review question. The QUADAS-2 tool considers four domains: patient selection, index test(s), reference standard and flow of patients through the study and timing of the tests. Randomised controlled trials (RCTs) evaluating the clinical impact of MRI-based technologies will be assessed using the Cochrane Risk of Bias 2.0 tool.[44] National Institute of Health study quality assessment tools[45] for cohort studies, case-control studies and before-after (pre-post) studies with no control group will be used to assess risk of bias of included non-randomised studies. Quality assessment of the included studies will be undertaken by one reviewer and checked by a

second reviewer. Any disagreements will be resolved by discussion and, if necessary, in consultation with a third reviewer.

3.6 Methods of analysis/synthesis of DTA studies

3.6.1 Statistical analysis and data synthesis

Individual study results

The sensitivity and specificity of each index test from DTA studies will be summarised using forest plots and plotted in receiver operating characteristic (ROC) space.

Meta-analysis

If meta-analysis is appropriate given the number of studies and extent of clinical heterogeneity, the EAG will use a bivariate model to obtain pooled estimates of the sensitivity and specificity of MRI-based technologies compared to liver biopsy as the reference standard.[46] Pooled estimates of sensitivity and specificity will be plotted in ROC space with a 95% confidence region around this summary estimate.

Where data are sparse or if few studies are identified, the EAG will reduce the bivariate model to two univariate random-effects logistic regression models by assuming no correlation between sensitivity and specificity across studies.[47]

In the first instance, the EAG will adopt a conservative approach and perform meta-analysis using random-effects. If study characteristics, populations and results are sufficiently homogenous, the EAG will perform an additional meta-analysis using fixed-effects (i.e., simplifying the regression models to fixed-effects models by eliminating the random-effects parameters for sensitivity and specificity).

The bivariate model will be fitted using the metandi command in Stata version 14 or the mada package in R version 4.0.2, or using the xtmelogit command in Stata version 14 if data are sparse. If meta-analysis is not possible, the results of the included studies will be synthesised narratively.

3.6.2 Subgroup analyses

If data are available, the impact of the following variables on the diagnostic accuracy of MRI-based technologies will be examined by performing subgroup analyses or meta-regression (by inclusion of the variable as a covariate in a bivariate model):

- prior tests for fibrosis (i.e., an indicator variable for whether FIB-4, NFS, ELF, TE and/or ARFI tests have previously been performed)

- age (i.e., adults [≥18 years] compared to children and young people [<18 years] and/or mean / median age of patients in the study included as a continuous covariate in the bivariate model).

3.6.3 Sensitivity analyses

If data are available, sensitivity analyses will be conducted by excluding studies judged to have a high risk of bias for at least one domain of the QUADAS-2 tool, or if the EAG is uncertain about the appropriateness of including them in the primary meta-analyses.

3.7 Methods of analysis/synthesis of clinical impact studies

Clinical and intermediate outcome data (see Table 2) will be tabulated or plotted. Binary or categorical data will be presented as frequencies and proportions and continuous data will be presented as means and standard deviations, or medians and interquartile ranges, according to the distribution of the continuous data.

If meta-analysis of clinical and intermediate outcomes is possible, the EAG will use fixed-effect or random-effects models to pool effect measures as appropriate, depending on the extent of clinical heterogeneity present between the study characteristics, populations and results of included studies. Binary data will be pooled in a meta-analysis of proportions using the metaprop command in Stata version 14. Pooled proportions with 95% confidence intervals will be presented. Continuous data expressed as means and standard deviations or standard errors (calculated from standard deviations or confidence intervals where appropriate) will be pooled in an inverse-variance meta-analysis using the metan command in Stata version 14.

Clinical and methodological heterogeneity between the included studies will be assessed by considering differences in (a) study population, (b) interventions, (c) outcome measures, (d) study quality, and (e) study design. In addition, if pooling two or more studies including the same treatments in meta-analysis is possible and clinically meaningful, forest plots will be visually assessed for the presence of heterogeneity. Statistical heterogeneity will be assessed using the chi-square test and I^2 statistics. Depending on the level of clinical, methodological and statistical heterogeneity, subgroup and sensitivity analyses (as described in Section 3.6.2 and Section 3.6.3) will be carried out.

Results for the following outcomes may only be reported narratively: impact of test result on clinical decision making, uptake and maintenance of lifestyle modifications, and acceptability of different testing modalities.

3.8 Other considerations

After consideration of the available data, the inclusion of uncontrolled single-arm studies may be restricted to studies with at least 30 participants.

4 METHODS FOR ASSESSING COST EFFECTIVENESS

The economic evaluation will assess the cost effectiveness of MRI-based technologies compared to no further testing for fibrosis, inflammation or steatosis prior to deciding whether to do a liver biopsy in patients with NAFLD. The economic evaluation will include a review of existing economic evaluations of the diagnostic tests and the creation of a de novo economic model.

4.1 Systematic review of cost effectiveness evidence

A systematic review will be conducted to identify published full economic evaluations of diagnostic tools that have been used in clinical practice to assess liver fibrosis, inflammation and steatosis in patients with NAFLD. A search filter to identify economic evaluations will be applied to the clinical search strategies. The following electronic databases will be searched from inception until the latest available version for relevant studies:

- MEDLINE (via Ovid)
- MEDLINE Epub Ahead of Print and MEDLINE In-Process & Other Non-Indexed Citations (via Ovid)
- Embase (via Ovid)
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Central Database of Controlled Trials (CENTRAL)
- Database of Abstracts of Reviews of Effects (DARE) (via Centre for Reviews and Dissemination)
- Health Technology Assessment Database (HTA) (via International HTA Database)
- EconLit (EBSCO)
- Cost-Effectiveness Analysis (CEA) registry.

Separate targeted searches will be carried out to identify supporting information on costs and health state utility data. Study selection and data extraction will be carried out as described in Sections 3.3 and 3.4 respectively. The methodological quality of the full economic evaluations included in the review will be assessed using the consolidated health economic evaluation reporting standards (CHEERS) checklist.[48] A narrative synthesis and structured tables will be used to present the main findings from the economic evaluations included in the systematic review.

4.2 Development of a health economic model

An economic model will be developed, in collaboration with clinical experts, following the completion of the systematic review. The model will be used to generate estimates of the cost effectiveness of MRI-based technologies versus no further testing.

Clinical effectiveness and diagnostic accuracy estimates will be taken from the results of the systematic review described in Section **Error! Reference source not found.** or targeted literature searches if required to inform model parameters. Other model parameters (e.g., utilities and cost data) will be derived from targeted economic searches, routine data sources (e.g., NHS Reference Costs[49]) and expert opinion. All evidence will be evaluated according to the recommendations of the NICE Diagnostics Assessment Programme manual.[41]

4.2.1 Model structure

The structure of the model will take into consideration any previous economic models for people with NAFLD and other liver diseases. It is anticipated that the event pathways will be modelled by a decision tree to estimate short-term outcomes including results of the diagnostic tests, followed by a Markov cohort structure to model long-term costs and benefits. The economic model will incorporate the pathways of care that individuals follow under standard practice in the UK NHS and for which credible evidence is available. The EAG will seek expert clinical advice to help structure the diagnostic and care pathways, i.e., with and without LiverMultiScan and/or MRE. The final model structure will depend on the findings from the literature reviews and consultation with clinical experts and may, therefore, evolve over time.

The population considered in the model will be people with NAFLD presenting to secondary and tertiary care settings with NAFLD for whom advanced fibrosis or cirrhosis has not been diagnosed. The following subgroups will be considered:

- patients who have indeterminate results from fibrosis testing
- patients for whom transient elastography or ARFI is unsuitable
- patients who have discordant results from fibrosis testing.

If data allow, the model will consider the impact of the test results on:

- decisions about the need for a biopsy
- offering of targeted lifestyle interventions
- adherence to lifestyle advice
- the extent of monitoring offered.

The economic assessment will be undertaken from the perspective of the NHS and Personal Social Services. The model time horizon will be set to patient lifetime and both costs and benefits will be discounted at 3.5% per annum.

Model cost effectiveness results will be presented as incremental costs per quality adjusted life year (QALY) ratios.

Sensitivity analyses will be carried out to assess the robustness of the EAG's base case cost effectiveness results to realistic variations in the levels of the underlying parameter values.

For deterministic sensitivity analyses, parameters will be varied around the confidence intervals/credible intervals for each parameter where available, or by ±25% of the base case value if estimates of variance for the parameter are not available.

Probabilistic sensitivity analysis will be performed using distributions drawn from trial or published sources where available, or assumed where not available, for all appropriate model parameters.

Scenario analyses will also be used to explore any structural uncertainties that are identified during construction of the EAG's model, or where alternative plausible parameter values are identified.

5 OTHER INFORMATION

5.1 Handling information from the companies

Data submitted by the manufacturers will only be considered if received by the EAG no later than 26th January 2022. Data arriving after this date will not be considered. Any data that meet the inclusion criteria stated in Table 2 will be extracted and quality assessed as described in the methods section of this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by manufacturer name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. All confidential data used in the EAG cost effectiveness model will also be highlighted.

5.2 Project timetable

Milestones	Date to be completed
Draft protocol	7th September 2021
Final protocol	1st October 2021
Progress report	3rd January 2022
Draft assessment report	23rd February 2022
Final assessment report	23rd March 2022

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7 APPENDICES

7.1 Appendix 1 Draft search strategy (MEDLINE)

1 exp Non-alcoholic Fatty Liver Disease/
2 non-alcoholic fatty liver disease.tw,kw.
3 NAFLD.tw,kw.
4 non-alcoholic steatohepatitis.tw,kw.
5 NASH.tw,kw.
6 metabolic dysfunction associated fatty liver disease.tw,kw.
7 MAFLD.tw,kw.
8 or/1-7
9 exp Magnetic Resonance Imaging/
10 MRI.tw,kw.
11 magnetic resonance imagi*.tw,kw.
12 LiverMultiScan.tw,kw.
13 Magnetic resonance elastography*.tw,kw.
14 MRE.tw.kw.
15 or/9-14
16 8 and 15
17 exp animals/
18 human/
19 17 not 18
20 16 not 19
21 limit 20 to English language