NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Sponsor submission of evidence:
Evaluation title: Virtual Touch Quantification to diagnose and monitor liver fibrosis
Sponsor: Siemens
Date sections A and B submitted:
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Instructions for sponsors

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Medical Technologies Evaluation Programme process for developing NICE medical technologies guidance. Use of the submission template is mandatory.

The purpose of the submission is for the sponsor to collate, analyse and present all relevant evidence that supports the case for adoption of the technology into the NHS in England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Medical Technologies Evaluation Programme Methods guide' and the 'Medical Technologies Evaluation Programme Process guide' available at www.nice.org.uk/mt. After submission to, and acceptance by, NICE, the submission will be critically appraised by an External Assessment Centre appointed by NICE.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 11 of this document 'Related procedures for evidence submission'.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level

of detail requested, but that is considered to be relevant to the case for adoption. Appendices will not normally be presented to the Medical Technologies Advisory Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the economic evidence section with ‘see appendix X’.

All studies and data included in the submission must be referenced. Identify studies by the first author or trial ID, rather than by relying on numerical referencing alone (for example, ‘Trial 123/Jones et al.[126], rather than ‘one trial[126]’).Please use a recognised referencing style, such as Harvard or Vancouver.

The sponsor should provide a PDF copy of full journal articles or reports – in electronic or hard copy form – included in the submission, if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. This clearance must be wide enough to allow NICE to make further copies, store the article electronically for a limited period of time on a shared drive to be accessed by a limited number of staff. Additionally, any full article obtained and submitted in electronic format must be done so in a manner compliant with the relevant contractual terms of use permitting the sponsor electronic access to the article. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished research. NICE will then itself obtain full copies of all relevant papers or reports, paying a copyright fee where necessary. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked 'Response' or in the tables as appropriate. 'Response' text may be deleted.

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Glossary of terms

ARFI - Acoustic Radiation Force Impulse imaging - A method of measuring tissue elasticity including liver stiffness by way of shear wave speed using a multipurpose diagnostic ultrasound imaging machine.

Fibroscan- Transient elastography (FibroScan) is a non-invasive method of assessing liver fibrosis by measuring liver stiffness based on a mechanical wave generated by vibration.

Liver Biopsy- A surgical procedure that removes a sample of liver tissue for examination in a laboratory.

Virtual Touch™ Tissue Quantification (VTq) – is an implementation of Acoustic Radiation Force Impulse (ARFI) technology on a traditional ultrasound system

Section A – Decision problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues.

Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1 Statement of the decision problem

	Draft scope issued by NICE	*Variation from scope*	*Rationale for variation*
Population	*Virtual Touch Quantification is intended for use in adults or children with chronic hepatitis B or C in whom assessment of liver fibrosis is indicated.*		
Intervention	*The Virtual Touch Quantification (VTq) software application used with the Siemens Virtual Touch Tissue Imaging systems (the Acuson S2000 or S3000 ultrasound platforms)*		
Comparator(s)	*Transient elastography (Fibroscan)*		
	Liver biopsy	*Index test*	
Outcomes	*Correlation in assessment of stage of liver disease*	*Equivalent to below as index test is LB*	

	Correlation in assessment of stage of fibrosis using Metavir score		
	Sensitivity and specificity (using AUROC) in assessment of liver fibrosis		
	Use of anti-viral drugs	*2ry outcome*	
	Quality of life measures		
	Hospital bed usage and length of stay	*2ry outcome*	*function of accuracy of VTq*
	Requirement of liver biopsy	*2ry outcome*	*function of accuracy of VTq*
	Device-related adverse events	*Reviewed seperately*	
Cost analysis	*The cost analysis should include both FibroScan transient elastography and liver biopsy as comparators depending on which ofthese represents standard care in the relevant patient population. The use in both primary and secondary care settings should be considered.*		
	Scenarios considered in the model should include settings where there is a compatible Siemens		

	ultrasound machine and those without.		
	Costs will be considered from an NHS and personal social services perspective.		
	The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared.		
	Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.		
Subgroups to be considered	*None*		
Special considerations, including issues related to equality	*None*		

2 Description of technology under assessment

2.1 Give the brand name, approved name and details of any different versions of the same device.

Virtual Touch™ Tissue Quantification (Siemens Healthcare) is an implementation of Acoustic Radiation Force Impulse (ARFI) technology on a traditional ultrasound system. It is available as an additional option on their ACUSON S2000™ and S3000™.

2.2 What is the principal mechanism of action of the technology?

The Virtual Touch Quantification (VTq) (Siemens) software application assesses the stiffness of liver tissue through measurement of shear wave speed. (i Benson 2012)

The VTq software uses acoustic radiation force impulse (ARFI) imaging technology to measure the elasticity of tissue. An area of interest is first identified during a conventional ultrasound scan. An acoustic 'push pulse' is applied lateral to the location to generate a shear wave. The speed of the shear wave is proportional to the stiffness of the tissue. The VTq investigation comprises multiple measurements and is non-invasive and painless. A statistical summary of the median and mean shear wave velocities are reported by the software. The reliability of VTq measurements is usually confirmed by calculating the ratio of the inter-quartile range to median, which should be less than 0.30.

A VTq test adds 5-10 minutes to a routine abdominal ultrasound scan or it can be performed as a stand-alone test, taking around 15 minutes. An ultrasonographer , radiologist or hepatologist may perform the test which will normally be interpreted and reported by a radiologist or hepatologist.

3 Clinical context

3.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE.

Hepatitis refers to the inflammation of the liver. Acute hepatitis may resolve without causing permanent damage to the liver. It can, however, persist for many years (chronic hepatitis) causing scarring of the liver (fibrosis), and in the most serious cases cirrhosis resulting in loss of liver function (liver failure), which can be fatal. Chronic hepatitis is categorised according to the extent of liver damage, as mild, moderate, or severe (where severe refers to cirrhosis).

The Metavir score has been developed to describe the development of fibrosis. Fibrosis score: F0 = no fibrosis F1 = portal fibrosis without septa F2 = portal fibrosis with few septa F3 = numerous septa without cirrhosis F4 = cirrhosis.

Hepatitis may be caused by a number of different disease processes including infection of the liver by the hepatitis viruses.

The present evaluation looks at the assessment of fibrosis in patients with chronic infections of hepatitis B and/or C virus. The evaluation and assessment of patients with chronic disease is important as it guides antiviral therapy. The goal of treatment for chronic hepatitis B and C is to prevent cirrhosis, hepatocellular carcinoma (HCC) and liver failure. The incidence of HBV is around 25% that of HCV and it accounts for 20% of annual reported cases in England. [ii].

Liver biopsy is considered the gold standard for assessing liver fibrosis for both hepatitis B and C. Histological assessment uses the METAVIR score, based on an assessment of fibrosis and the degree of liver architecture disorganisation and classifies the severity of liver disease from none (grade F0) through mild, moderate, severe to cirrhosis (grade F4).

Elastography measurements, whether VTq or Transient Elastography are continuous variables and results are given a fibrosis score based on cut off values recommended by the supplier or determined by the user. This review

looks at the accuracy of VTq to describe the fibrosis state as assessed by biopsy. In some circumstances, for example the follow up of therapy the monitoring of the variable, in the case of VTq the measured shear wave speed, has been shown to have advantages. (xi.Yamada et al 2014)

Prevalence Hepatitis B:- NICE clinical guideline (published June 2013) CG165 Hepatitis B (chronic): Diagnosis and management of chronic hepatitis B in children, young people and adults states that approximately 19 people test positive for chronic hepatitis B per 100,000 population. The British Liver Trust currently reports the number of people in the UK with HBV as 325,000. [ii] It has been estimated that 96% of new cases of HBV infection are in migrants. (iii)

Prevalence Hepatitis C: There were 7,834 reported new cases of hepatitis C in England during 2010, but the true figure is likely to be higher. It is estimated that around 255,000 people in England have hepatitis C. Between 10% and 40% of people with untreated chronic hepatitis C develop cirrhosis. [iii]

The true prevalence of HCV is difficult to establish and likely to be underestimated because many people do not have symptoms. There are 6 major genotypes and several subtypes of HCV, the prevalence of each vary geographically. People can be infected with more than one genotype. The most recent national estimates (2013) suggest that 215,000 people are chronically infected with HCV in the UK, and that most of this infection (approximately 90%) is genotype 1 and genotype 3. However, more than half of people with chronic hepatitis C are unaware of their infection. Injecting drug users account for 49% of cases in England. [iv]

The prevalence of fibrosis in patients who have either Hepatitis B or C virus infection is difficult to assess. Age and the point at which the patient was diagnosed with viral hepatitis post infection are key factors. A significant proportion of patients with hepatitis were born outside the UK and therefore the patient mix seen at a clinic will determine the prevalence of fibrosis.

3.2 Give details of any relevant NICE or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies specific subgroups

and make any recommendations for their treatment. If available, these should be UK based guidelines.

NICE clinical guideline (published June 2013) CG165 Hepatitis B (chronic): Diagnosis and management of chronic hepatitis B in children, young people and adults Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection.

NICE public health guidance 43 (2012) Hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults. Hepatitis B and C guidance 43 encourages the local commissioning of integrated services for hepatitis B and C testing and treatment

NICE clinical guideline 165 (2013) Hepatitis C: diagnosis and management of Hepatitis C TBC NICE has taken the decision to pause the development of the clinical guideline for Hepatitis C until NICE technology appraisals evaluating new pharmacological therapies have published.

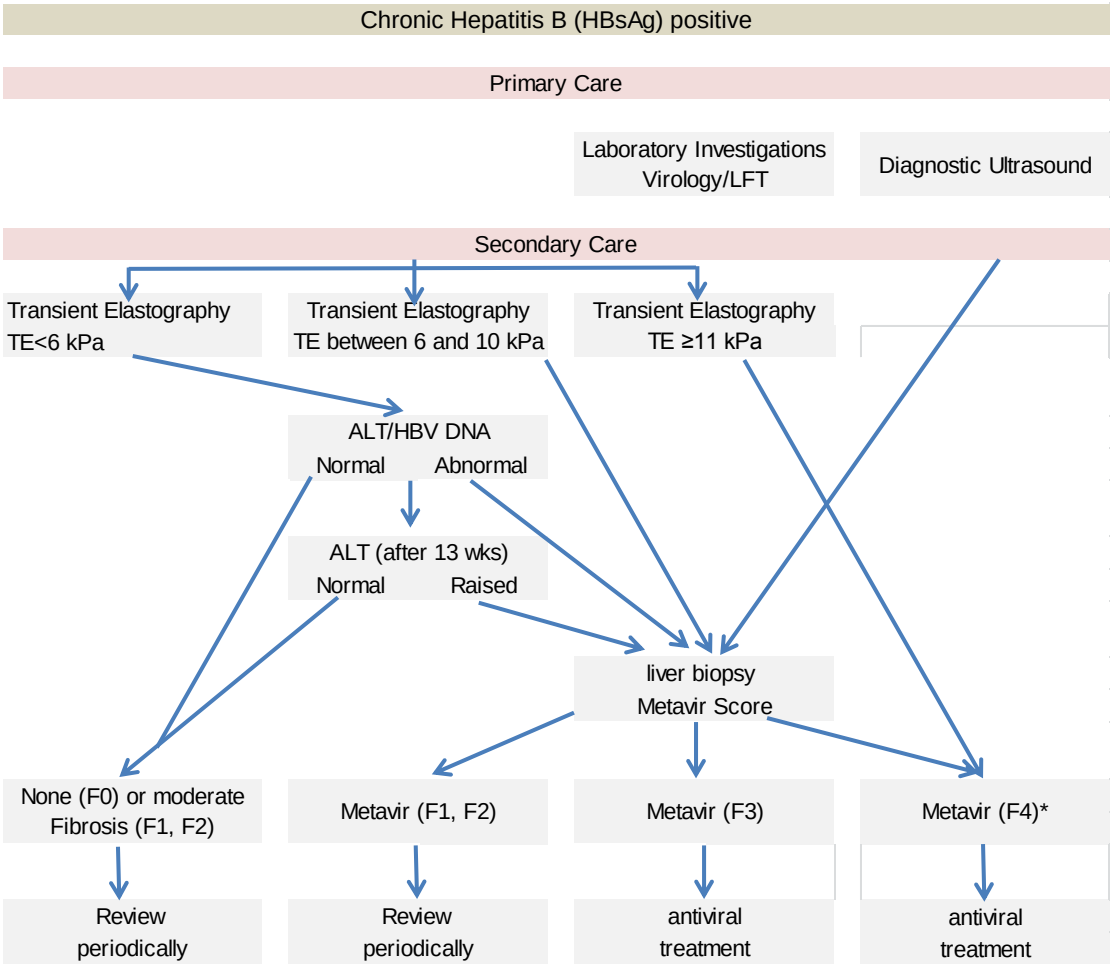
3.3 Describe the clinical pathway of care that includes the proposed use of the technology.

Hepatitis B (NICE Guideline)

HBsAg positive adults which describe those with chronic hepatitis should be referred to the relevant specialist in secondary care (hepatologist, gastroenterologist or infectious disease specialist with an interest in hepatology). On presentation in primary care a selection of virology and liver function tests are performed and an ultrasound scan to identify HCC performed. These are forward with the referral. The NICE guideline recommends that adult patients are offered transient elastography (FibroScan) as an initial test for chronic liver disease. Where this isn't available patients will receive a liver biopsy where this is viewed as clinically appropriate.

- *Offering antiviral treatment (without a liver biopsy) to patients with a transient elastography score ≥11 kPa*
- *Considering liver biopsy in patients with a transient elastography score between 6 and 10 kPa.*
- *Offering liver biopsy to patients with a transient elastography score < 6 kPa if they are <30 years and have HBV DNA >2000 IU/ml and abnormal ALT on 2 consecutive tests conducted 3 months apart*
- *Annual reassessment of patients who are not taking antiviral treatment.*

FIGURE A2 CURRENT DIAGNOSTIC ALGORITHM FOR ASSESSING FIBROSIS IN CHRONIC HEPATITIS B



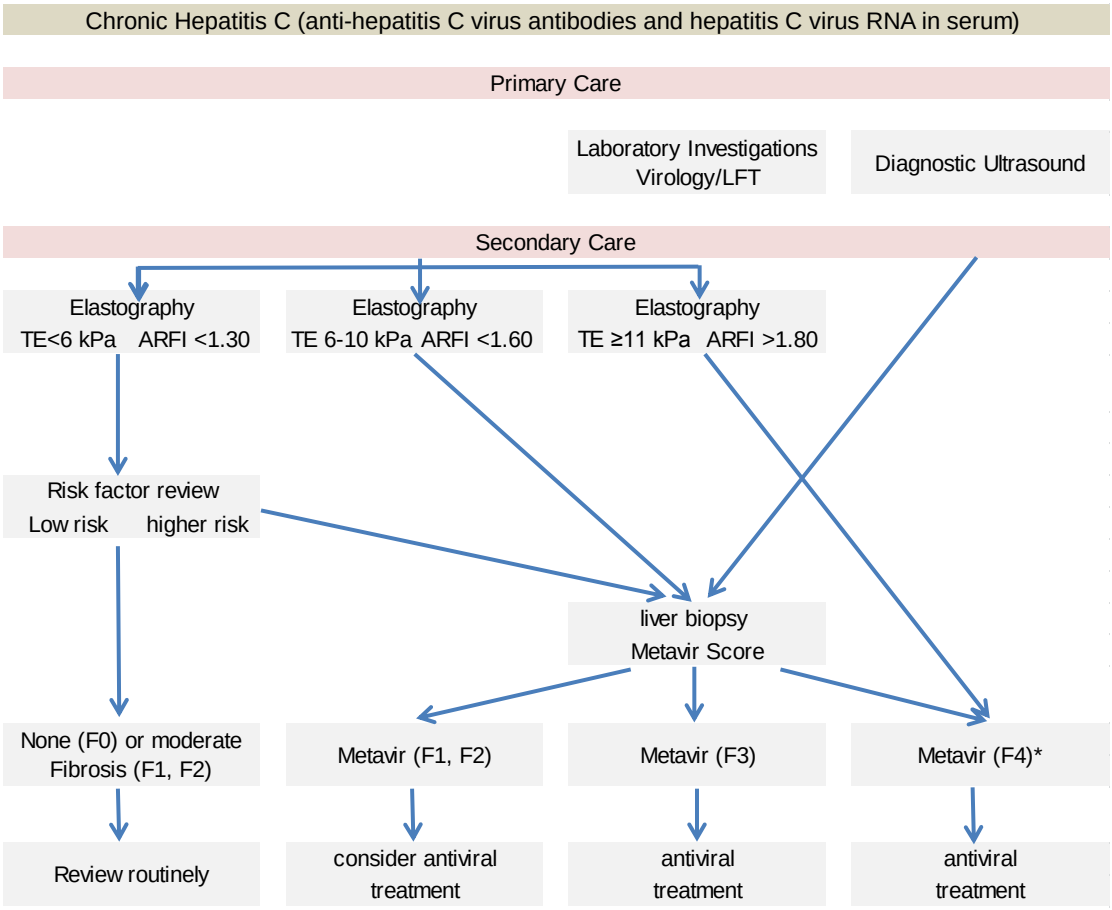
* or equivalent when not assessed by biopsy

Note: Primary care refers to the place where exams are requested

Hepatitis C

Patients who are hepatitis C RNA positive on a blood test are referred to a hepatology clinic. The degree of fibrosis is assessed and treatment options are discussed depending on specific patient contraindications and degree of liver disease.

FIGURE A3 DIAGNOSTIC ALGORITHM FOR CHRONIC HEPATITIS C



* or equivalent when not assessed by biopsy

3.4 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

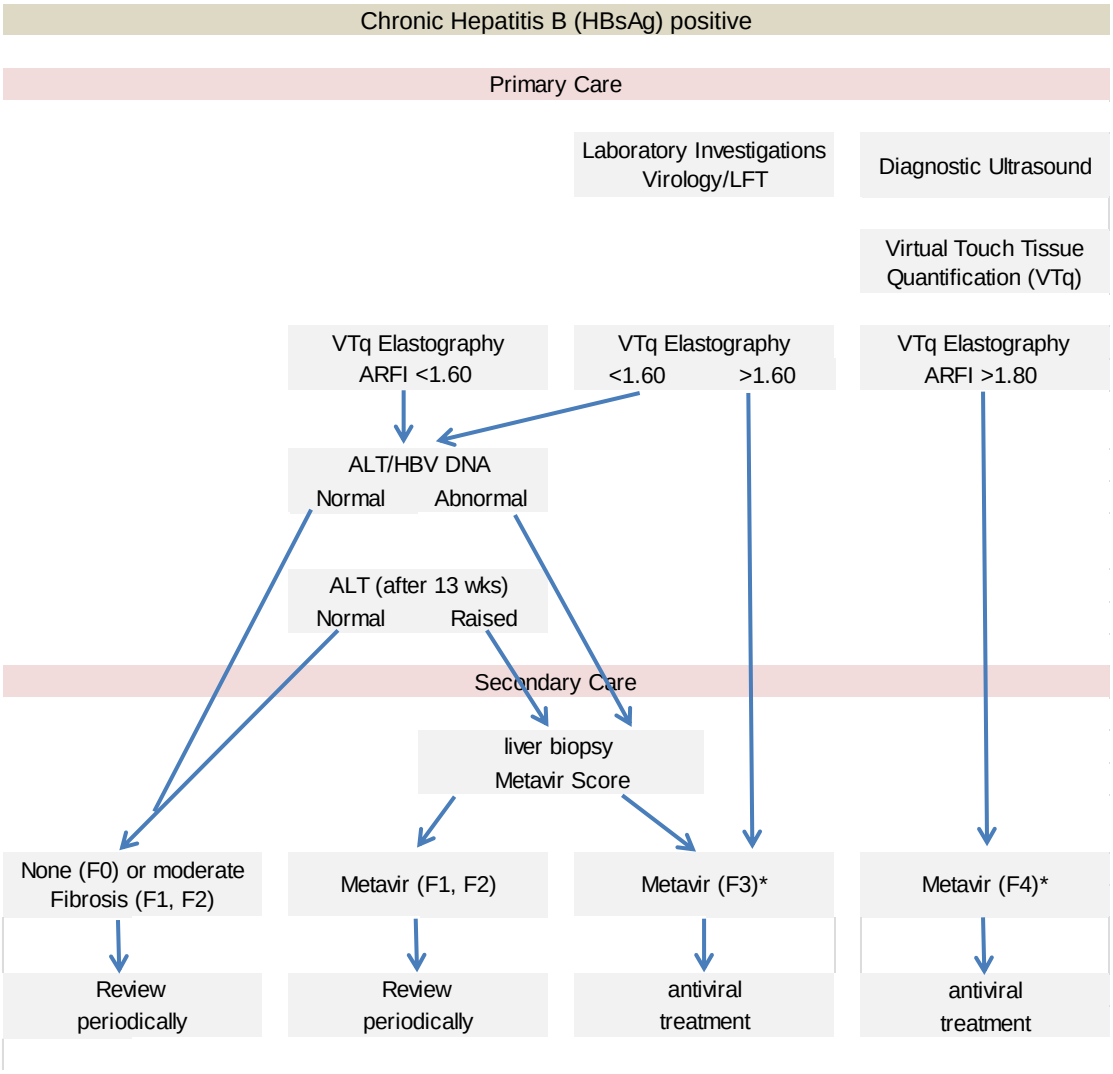
Hepatitis B

Current clinical practice may deviate from the recommended NICE guideline. Transient elastography is not offered in all secondary and tertiary centres. In 2013 according to the manufacturer there were 134 Fibroscan devices in use in the UK at 70 hospitals. VTq is available in 28 hospitals and in some of these locations it is used to determine the extent of fibrosis following viral infection. In all other centres biopsy is the only available technique to assess the extent of fibrosis. Liver biopsy conveys a small but significant risk or morbidity and mortality (1/10000). Liver biopsy requires at a minimum day case admission which can cause significant anxiety and inconvenience to the patient.

3.5 Describe the new pathway of care incorporating the new technology that would exist if the technology was adopted by the NHS in England.

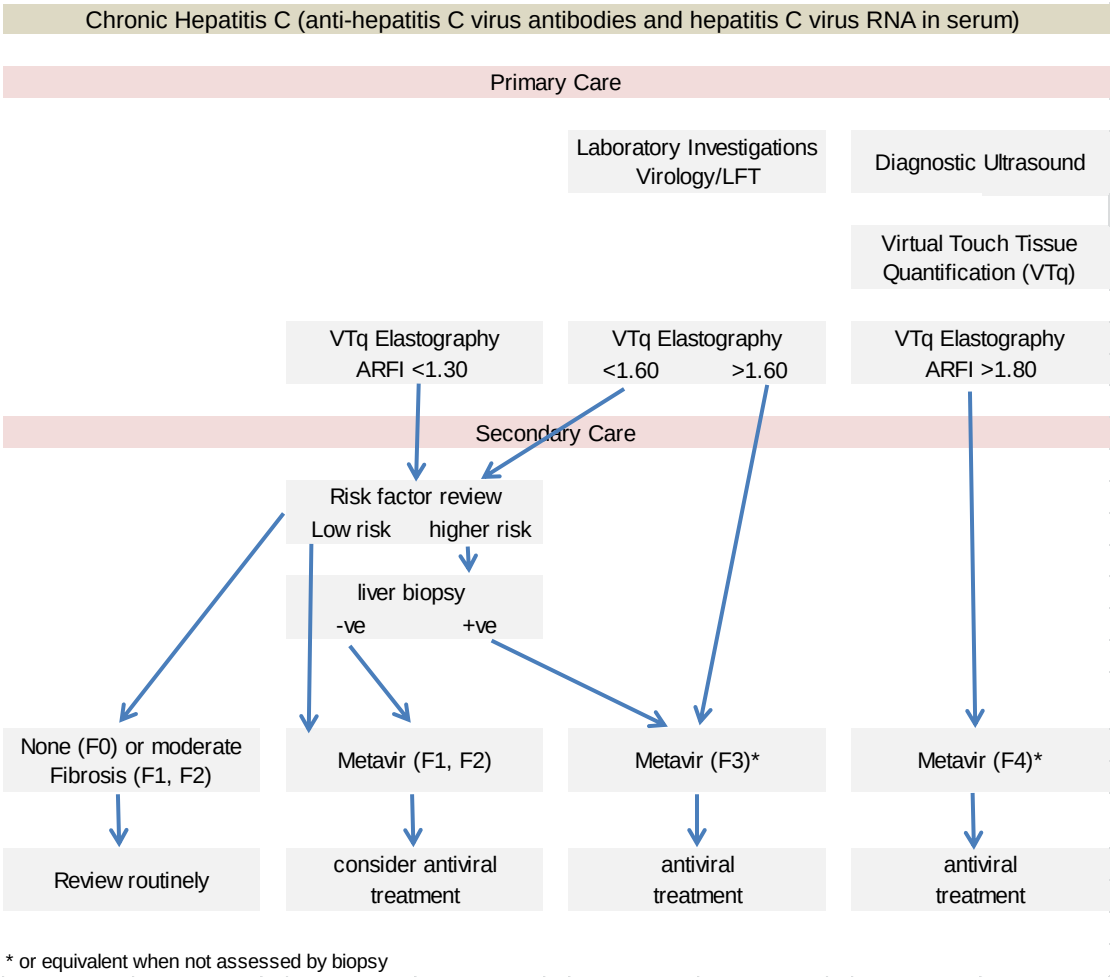
The new pathway will allow the GP request for liver elastography to be made at the same time as the request for laboratory and diagnostic ultrasound examinations. It offers the opportunity for patients to be triaged in primary care rather than all being referred for a consultant appointment.

FIGURE A4 NEW DIAGNOSTIC ALGORITHM FOR CHRONIC HEPATITIS B



* or equivalent when not assessed by biopsy

FIGURE A5 NEW DIAGNOSTIC ALGORITHM FOR CHRONIC HEPATITIS C



* or equivalent when not assessed by biopsy

3.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

Fibroscan and VTq are safer, painless and more cost efficient compared to liver biopsy.

- *No hospital stay or post procedure monitoring is required because the procedure can be performed in an outpatient setting.*
- *Serial biopsies over several years may be avoided to monitor fibrosis progression, therefore improving a patient's quality of life.*
- *VTq and Fibroscan are not consultant-led procedures.*

The VTq procedure offers advantages over Fibroscan.

- *The clinical evidence (Part B) highlights that VTq has a similar accuracy to Fibroscan.*
- *VTq offers the opportunity to use existing ultrasound equipment*
- *A more complete assessment of the liver can be achieved when VTq is used as the initial sonogram provides visualization of the liver parenchyma, portal and hepatic veins, portal and hepatic venous and arterial blood flow measurements, and visualization of the biliary tree for possible obstructions.*
- *The assessment can be made at the same appointment and on the same ultrasound scanner as screening for Hepatic Cellular Carcinoma (HCC) and so improving the patient experience.*
- *Certain features observed on ultrasound are highly specific for predicting severe fibrosis or cirrhosis (surface nodularity: specificity 95%; caudate lobe hypertrophy: 91%), but are not very sensitive (sensitivity of 54% and 41% respectively)[v Coli A 2003]. The addition of VTq allows for improved diagnosis while visual control of measurement location allows the operator to:*
    - *avoid vascular structures when taking measurements*
    - *study regions of interest (area of steatosis, liver with tumor)*

- *select the measurement depth*
- *can be used in patients with Ascites*
- *can be used in patients with a high BMI*

- *Earlier identification of fibrosis in patients with viral hepatitis should allow earlier intervention with anti-viral drugs, which can reverse the course of early disease*

3.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

None

3.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

None

3.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

- *Biopsy number reduced (see part C Economic Analysis) with resultant cost savings.*
- *Fibroscan (see part C Economic Analysis) with resultant cost savings.*

3.10 Describe how the NHS in England can disinvest from tests, investigations, interventions, facilities or technologies described in section 3.9 that would no longer be needed with using this technology.

Reduced resource costs

VTq takes place in an outpatient setting and therefore the patient will not require to be admitted and potentially remain overnight in hospital.

VTq can be used as an alternative to Transient Elastography where this is not available.

A number of patients who are referred for liver biopsy do not attend the appointment (we have not ascertained the actual proportion of 'no shows) and this is costly both in terms of the missed appointment cost but also the future cost of treating fibrosis which has increased in severity.

4 Regulatory information

4.1 Provide PDF copies of the following documents:

- instructions for use
- CE mark certificate or equivalent UK regulatory approval such as EC declaration of conformity
- quality systems (ISO 13485) certificate (if required).

Included are:

- *Acuson S Family Features and Applications Manual. PDF*
- *VT Tissue Quantification Scan Technique*
- *Strain Imaging in the Abdomen. PDF*
- *CE mark certificate for the Acuson S2000 and S3000*
- *The ACUSON S2000 and S3000 platform is in compliance with ISO 13485*

4.2 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The Acuson S2000 and S3000 equipped with or without Virtual Touch Quantification has a CE mark Class II since 2008.

4.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

The device is approved in a number of countries including the USA where it has received 510(k) K131164

4.4 If the technology has not been launched in the UK provide the anticipated date of availability in the UK.

The technology is already available in the UK

4.5 If the technology has been launched in the UK provide information on the use in England.

There are 28 Acuson S2000 and S3000 with VTq capability in the UK NHS (26 in NHS England).

5 Ongoing studies

5.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

We have not been made aware of any on going studies

If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

Currently there is no other form of assessment planned in the UK

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in section 11.3 of this document.

6.1.1 Describe any equality issues relating to the patient population and condition for which the technology is being used.

This is not part of the scope of the evaluation. Replacing a biopsy measurement with a non-invasive measurement will be extremely beneficial in younger populations.

6.1.2 Describe any equality issues relating to the assessment of the technology that may require special attention.

Not applicable.

6.1.3 How will the submission address these issues and any equality issues raised in the scope?

Not applicable

Section B – Clinical evidence

7 Published and unpublished clinical evidence

Section B requires sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read section 6 of the Medical Technologies Evaluation Programme methods guide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in table A1.

Sponsors are required to submit section B in advance of the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

7.1 Identification of studies

Published studies

7.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in section 10, appendix 1.

Search strategies were based on the target condition (hepatitis) the intervention (VTq) the comparator (Fibroscan) and the index test liver biopsy.

Unpublished studies

7.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

As the manufacturer of the software we believe we are kept well informed by our users of research which they are undertaking.

7.2 Study selection

Published studies

7.2.1 Complete table B1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table B1 Selection criteria used for published studies

Inclusion criteria	
Population	Hepatitis B or C
Interventions	ARFI using VTq
Outcomes (Primary)	Correlation in assessment of stage of liver disease
	Sensitivity and specificity (using AUROC) in assessment of liver fibrosis
	Correlation in assessment of stage of fibrosis using Metavir score
Study design	Test accuracy studies
Language restrictions	Abstract in English
Search dates	2009- 2014 Present
Exclusion criteria	
Population	Undefined Hepatic/Liver Fibrosis
Interventions	Liver biopsy and/or FibroScan transient elastography and/or ARFI using equipment other than AcusonS2000 or S3000
Outcomes	Accuracy measurements not provided
Study design	reviews, editorials, opinion pieces, case reports; studies reporting only technical aspects of the test; studies with < 10 participants
Language restrictions	No English Abstract
Search dates	N/a

7.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

See 7.24 PRISMA statement flow diagram for published and unpublished studies

Unpublished studies

7.2.3 Complete table B2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table B2 Selection criteria used for unpublished studies

Inclusion criteria	
Population	Hepatitis B or C
Interventions	ARFI using VTq
Outcomes (Primary)	Correlation in assessment of stage of liver disease
	Sensitivity and specificity (using AUROC) in assessment of liver fibrosis
	Correlation in assessment of stage of fibrosis using Metavir score
Study design	Test accuracy studies
Language restrictions	Abstract in English
Search dates	2007- 2014 Present
Exclusion criteria	
Population	Undefined Hepatic/Liver Fibrosis
Interventions	Liver biopsy and/or FibroScan transient elastography and/or ARFI using equipment other than AcusonS2000 or S3000
Outcomes	Accuracy measurements not provided
Study design	reviews, editorials, opinion pieces, case reports; studies reporting only technical aspects of the test; studies with < 10 participants
Language restrictions	No English Abstract
Search dates	N/a

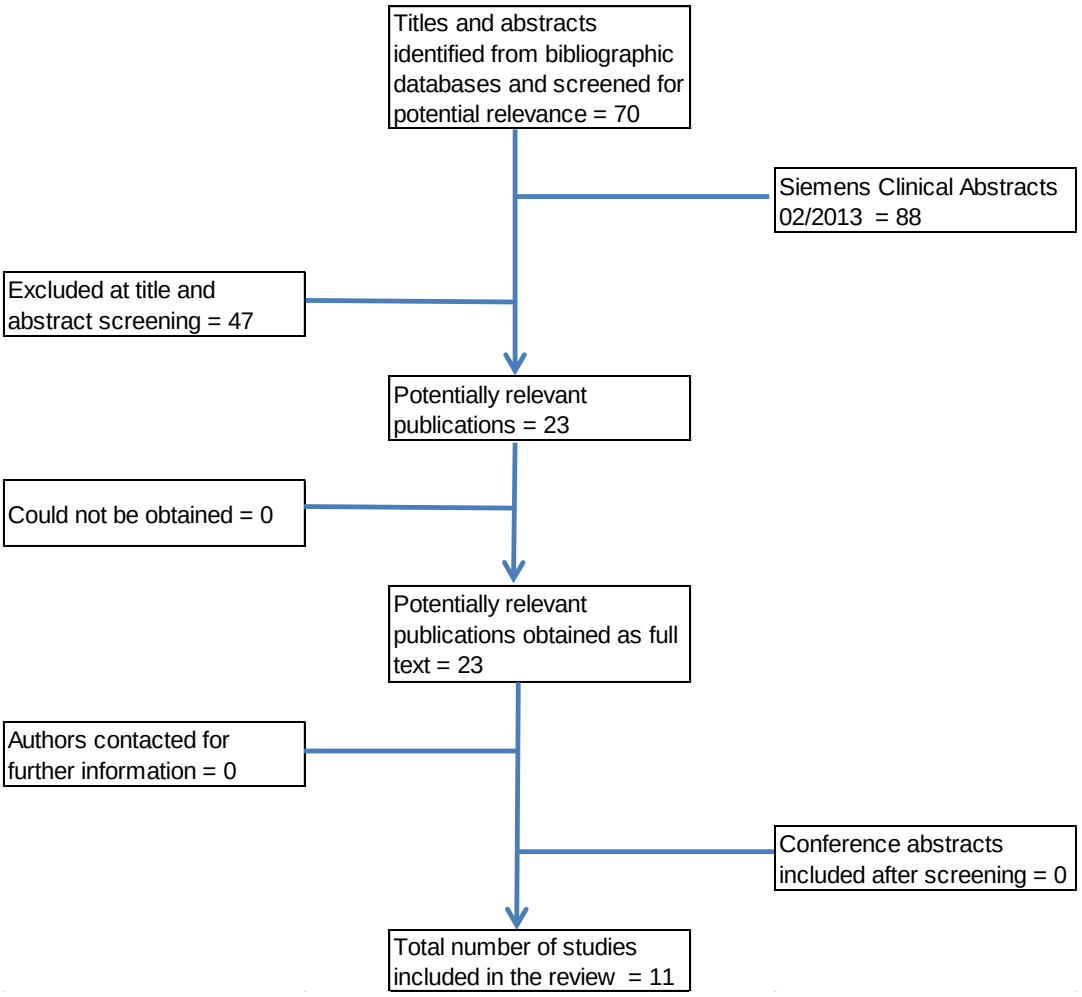
7.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

The literature searches of bibliographic databases identified 70 references. After initial screening of titles and abstracts, 23 were considered to be potentially relevant and subjected to full-paper screening.

No additional studies were identified from searches of clinical trials registries.

FIGURE B1 shows the flow of studies through the review process

Figure B1 FLOW OF STUDIES THROUGH THE REVIEW PROCESS AFTER PRISMA



7.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished studies. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

7.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables B1 and B2.

23 publications were considered potentially relevant.

Table B3 List of relevant published studies

Ref	Study name	Population	Intervention	Comparator
2	Acoustic radiation force impulse-imaging in comparison to transient elastography for non-invasive assessment of liver fibrosis in chronic hepatitis C: A prospective international multicenter study	HCV (n=253)	ARFI	TE,LB
8	Acoustic radiation force impulse is better than transient elastography in assessing liver fibrosis in chronic hepatitis C using collagen proportionate area as reference	HCV (n=93)	ARFI	TE,LB
11	Analysis of risk factors for aiming at early detection of hepatocellular carcinoma	Mixed	ARFI	TE,LB
12	Non-invasive assessment of liver fibrosis: Acoustic radiatiation force impulse of the left lobe correlates best with ishak histology score	HBV (n=11), HCV (n=27), Other	ARFI	TE,LB
14	The feasibility of shear-wave elastographic methods for non-invasive assessment of liver fibrosis in chronic viral hepatitis patients	HBV (n=67), HCV (n=99)	ARFI	TE,LB?
17	Non-invasive assessment of liver fibrosis with acoustic radiation force imaging and transient elastography in chronic viral hepatitis	HBV (n =65), HCV (n = 83)	ARFI	TE,LB

21	Assessment of liver fibrosis with ARFI: Comparison with M and XL probes of Fibroscan and FibroTest in chronic liver diseases	HBV, HCV, Other (n=185)	ARFI	TE,LB
22	ARFI performance in the noninvasive assessment of HCV cirrhosis, compared to transient elastography and FIB score	HCV (n=200)	ARFI	TE,LB,Blood
25	Acoustic radiation force impulse imaging for non-invasive assessment of liver fibrosis in chronic hepatitis B	HBV (n=114)	ARFI	TE,LB
26	Acoustic Radiation Force Impulse Elastography for fibrosis evaluation in patients with chronic hepatitis C: An international multicenter study	HCV (n=914)	ARFI	TE,LB
31	ARFI elastography vs. transient elastography: Which one is more influenced by high aminotransferases values	HBV (n=73), HCV (n=153), Other	ARFI	TE,LB
33	Comparison of liver stiffness values by virtual touch ARFI and fibroscan TE in large sample study of 554 cases	HBV, HCV	ARFI	TE
34	Comparative Study Concerning the Value of Acoustic Radiation Force Impulse Elastography (ARFI) in Comparison with Transient Elastography (TE) for the Assessment of Liver Fibrosis in Patients with Chronic Hepatitis B and C	HBV (n=53), HCV (n=107)	ARFI	TE,LB
38	Which elastographic method (transient elastography or ARFI) is more useful for liver fibrosis evaluation in patients with chronic hepatitis C? An international multicenter study	HCV (n=377)	ARFI	TE,LB

44	Performance of Acoustic Radiation Force Impulse imaging for the staging of liver fibrosis: A pooled meta-analysis	Mixed	ARFI	TE,LB
45	Acoustic radiation force impulse imaging (ARFI) for non-invasive detection of liver fibrosis: Examination standards and evaluation of interlobe differences in healthy subjects and chronic liver disease	HCV (n = 69), Other	ARFI	TE,LB
47	Is it better to use two elastographic methods for liver fibrosis assessment?	HCV (n = 197)	ARFI	TE,LB
52	Comparison of transient elastography (TE) and acoustic radiation force impulse (ARFI) for noninvasive staging of liver fibrosis in patients with chronic hepatitis C	HCV	ARFI	TE,LB
55	Which is the best noninvasive ultrasound method for the evaluation of liver fibrosis?	HBV (N=17), HCV (N=54)	ARFI	TE,LB
61	Performance of a new elastographic method (ARFI technology) compared to unidimensional transient elastography in the noninvasive assessment of chronic hepatitis C. Preliminary results	HCV	ARFI	TE,lb
57	Performance of Acoustic Radiation Force Impulse imaging in the noninvasive assessment of liver fibrosis, in comparison to unidimensional transient elastography	HCV	ARFI	TE,LB
48	How efficient is acoustic radiation force impulse elastography for the evaluation of liver stiffness?	Unclear	ARFI	TE,LB

18	Meta-analysis: ARFI elastography versus transient elastography for the evaluation of liver fibrosis	META	ARFI	META

Table B4 List of relevant unpublished studies

We have not identified any unpublished studies and therefore we have not completed TABLE B4 LIST OF RELEVANT UNPUBLISHED STUDIES

7.3.2 State the rationale behind excluding any of the published studies listed in tables B3 and B4.

Of the 23 publications considered potentially relevant.

12 studies reported as conference abstracts, did not contain sufficient information to complete the inclusion assessment. Based on the searches and inclusion screening described above, 11 studies were included in the review.

Time constraints have prevented us from contacting the authors of papers when there was insufficient information for full assessment.

7.4 Summary of methodology of relevant studies

The included studies were test accuracy studies.

1 concerned the use of ARFI and TE on patients with Hepatitis B (25)

5 concerned the use of ARFI and TE on patients with Hepatitis C (2,26,47,52,61)

3 concerned the use of ARFI and TE on patients with Hepatitis B and C where results for both infections were separately reported (34,44,55)

2 concerned the use of ARFI and TE on patients in which Hepatitis B and C comprised a substantial proportion of studies but where results for all causes of fibrosis were grouped. (45,48)

All included studies were published in 2009 or later. All of the included studies were conducted in Europe (the majority in Germany and Romania).

1 study reported funding (speakers expenses) from the manufacturer of VTq and 4 studies did not report any information on funding sources. (2,34,47,52)

7.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables B5 and B6 as appropriate. A separate table should be completed for each study.

Table B5 Summary of methodology for randomised controlled trials

There were no randomised control trials and therefore a table summarising these studies is not included

Table B6 Summary of methodology for observational studies

Reference Number	2
Study name	Acoustic radiation force impulse-imaging in comparison to transient elastography for non-invasive assessment of liver fibrosis in chronic hepatitis C: A prospective international multicenter study
Objective	compare ARFI and TE for the assessment of liver fibrosis in patients with chronic hepatitis C
Location	Multicentre
Design	Prospective
Duration	n/a
Population	HCV (n=253)
Sample size	253
Inclusion criteria	n/a
Exclusion criteria	n/a
Intervention(s) (n =) and comparator(s) (n =)	TE (247), ARFI (247), LB (247)
Baseline differences	N/a
followed-up	None
Statistical tests	n/a
Primary outcomes	Accuracy YES Correlation YES
Secondary outcomes	None

Table B6 Summary of methodology for observational studies

Reference Number	25
Study name	Acoustic radiation force impulse imaging for non-invasive assessment of liver fibrosis in chronic hepatitis B
Objective	evaluate ARFI for the assessment of liver fibrosis in chronic hepatitis B
Location	Multicentre - Germany, Netherlands
Design	median value of 10 valid measurements
Duration	2009-2010
Population	HBV (n=114)
Sample size	114
Inclusion criteria	88 incl
Exclusion criteria	Alcoholism
Intervention(s) (n =) and comparator(s) (n =)	TE 88, ARFI 88 vs LB All
Baseline differences	N/a
followed-up	None
Statistical tests	Spearman
Primary outcomes	Accuracy YES Correlation YES
Secondary outcomes	None

Table B6 Summary of methodology for observational studies

Reference Number	26
Study name	Acoustic Radiation Force Impulse Elastography for fibrosis evaluation in patients with chronic hepatitis C: An international multicenter study
Objective	evaluate the reliability of Acoustic Radiation Force Impulse (ARFI) elastography for predicting fibrosis severity
Location	Multicentre
Design	Mixed
Duration	n/a
Population	HCV (n=914)
Sample size	914
Inclusion criteria	unclear
Exclusion criteria	unclear
Intervention(s) (n =) and comparator(s) (n =)	TE, ARFI vs LB Numbers varied depending on sub group analysis
Baseline differences	N/a
followed-up	None
Statistical tests	Spearman
Primary outcomes	Accuracy YES Correlation YES
Secondary outcomes	None

Table B6 Summary of methodology for observational studies

Reference Number	34
Study name	Comparative Study Concerning the Value of Acoustic Radiation Force Impulse Elastography (ARFI) in Comparison with Transient Elastography (TE) for the Assessment of Liver Fibrosis in Patients with Chronic Hepatitis B and C
Objective	compare liver stiffness (LS) measurements by means of acoustic radiation force impulse (ARFI) elastography and transient elastography (TE) in patients with chronic hepatitis B and
Location	Romania
Design	10 valid ARFI and TE
Duration	2009-2011
Population	HBV (n=53), HCV (n=107)
Sample size	160
Inclusion criteria	146 (50C,96B), Homogeneous liver structure no ascites
Exclusion criteria	n/a
Intervention(s) (n =) and comparator(s) (n =)	TE 51B 105 C, ARFI 53 B 107 C vs LB All
Baseline differences	N/a
followed-up	None
Statistical tests	Spearman
Primary outcomes	Accuracy NO Correlation YES
Secondary outcomes	None

Table B6 Summary of methodology for observational studies

Reference Number	44
Study name	Performance of Acoustic Radiation Force Impulse imaging for the staging of liver fibrosis: A pooled meta-analysis
Objective	evaluate the overall performance of ARFI for the staging of liver fibrosis
Location	Multicentre - Romania, Japan, GermanyMETA
Design	Non uniform Varies depending on included study
Duration	2009-2010
Population	HBV (n = 51) HCV (n = 380)
Sample size	518
Inclusion criteria	
Exclusion criteria	n/a
Intervention(s) (n =) and comparator(s) (n =)	TE, ARFI vs LB All
Baseline differences	N/a
followed-up	None
Statistical tests	n/a
Primary outcomes	Accuracy YES Correlation CHECK
Secondary outcomes	None

Table B6 Summary of methodology for observational studies

Reference Number	45
Study name	Acoustic radiation force impulse imaging (ARFI) for non-invasive detection of liver fibrosis: Examination standards and evaluation of interlobe differences in healthy subjects and chronic liver disease
Objective	develop standards for ARFI
Location	Germany
Design	10 valid ARFI and TE
Duration	12 months - 2010-2011
Population	HCV (n = 69), Other
Sample size	116
Inclusion criteria	n/a
Exclusion criteria	Pregnancy, dilated bile ducts
Intervention(s) (n =) and comparator(s) (n =)	TE, ARFI vs LB All
Baseline differences	N/a
followed-up	None
Statistical tests	Spearman/Pearson
Primary outcomes	Accuracy NO Correlation NO
Secondary outcomes	None

Table B6 Summary of methodology for observational studies

Reference Number	47
Study name	Is it better to use two elastographic methods for liver fibrosis assessment?
Objective	combining 2 ultrasound based elastographic methods: acoustic radiation force impulse (ARFI) elastography and transient elastography (TE), we can improve the prediction of fibrosis in patients with chronic hepatitis C
Location	Romania (2 centres)
Design	10 LS measurements by TE and ARFI
Duration	n/a
Population	HCV (n = 197)
Sample size	197
Inclusion criteria	n/a
Exclusion criteria	other causes or chronic hepatitis
Intervention(s) (n =) and comparator(s) (n =)	TE (187), ARFI (191) vs LB All
Baseline differences	N/a
followed-up	None
Statistical tests	Spearman
Primary outcomes	Accuracy YES Correlation YES
Secondary outcomes	None

Table B6 Summary of methodology for observational studies

Reference Number	52
Study name	Comparison of transient elastography (TE) and acoustic radiation force impulse (ARFI) for noninvasive staging of liver fibrosis in patients with chronic hepatitis C
Objective	compare the performance and the discordance rate of Acoustic Radiation Force Impulse (ARFI) and TE with liver biopsy in a cohort of chronic hepatitis C patients
Location	Italy (Palermo and Catania)
Design	Prospective informed consent
Duration	2008 - 2009
Population	HCV
Sample size	139
Inclusion criteria	n/a
Exclusion criteria	Coinfection with HIV, antiviral therapy, alcohol abuse
Intervention(s) (n =) and comparator(s) (n =)	TE (130), ARFI (139) vs LB All
Baseline differences	N/a
followed-up	None
Statistical tests	
Primary outcomes	Accuracy YES Correlation YES
Secondary outcomes	None

Table B6 Summary of methodology for observational studies

Reference Number	55
Study name	Which is the best noninvasive ultrasound method for the evaluation of liver fibrosis?
Objective	which method that uses ultrasound waves is the best for the evaluation of liver stiffness (LS)
Location	Romania
Design	10 LS measurements by TE and ARFI
Duration	
Population	HBV (N=17), HCV (N=54)
Sample size	71
Inclusion criteria	
Exclusion criteria	
Intervention(s) (n =) and comparator(s) (n =)	TE, ARFI vs LB All
Baseline differences	N/a
followed-up	None
Statistical tests	Spearman
Primary outcomes	Accuracy YES Correlation YES
Secondary outcomes	None

Table B6 Summary of methodology for observational studies

Reference Number	61
Study name	Performance of a new elastographic method (ARFI technology) compared to unidimensional transient elastography in the noninvasive assessment of chronic hepatitis C. Preliminary results
Objective	Evaluate the performance of a compare (ARFI) withTE.
Location	Romania
Design	10 LS measurements by TE and ARFI
Duration	October and December 2008.
Population	HCV
Sample size	112
Inclusion criteria	positive HCV-RNA
Exclusion criteria	ascites, co-infection with HBV and/or HIV, other active infectious diseases, and pregnancy.
Intervention(s) (n =) and comparator(s) (n =)	TE(102), ARFI (102) vs LB All
Baseline differences	N/a
followed-up	None
Statistical tests	n/a
Primary outcomes	Accuracy YES Correlation YES
Secondary outcomes	None

Table B6 Summary of methodology for observational studies

Reference Number	48
Study name	How efficient is acoustic radiation force impulse elastography for the evaluation of liver stiffness?
Objective	As stated in title
Location	Romania
Design	10 TE and 5 ARF
Duration	Unclear
Population	Unclear
Sample size	223
Inclusion criteria	patients with chronic liver diseases and normal volunteers
Exclusion criteria	liver cirrhosis and ascites
Intervention(s) (n =) and comparator(s) (n =)	TE, ARFI vs LB
Baseline differences	N/a
followed-up	None
Statistical tests	Spearman
Primary outcomes	Accuracy YES Correlation YES
Secondary outcomes	None

We have not included any studies which were obvious duplicates. We expect that data in some of the earlier studies by the same author will have been included in later reports with larger study numbers. We expect that in the meta analysis papers data which has been previously reported is included.

7.4.2 Highlight any differences between patient populations and methodology in all included studies.

Bias and confounding factors

- *Steatosis can affect the result of TE measurements*
- *BMI can affect the result of TE and ARFI measurements*
- *The patient populations we have included are HBV, HCV, HBV and HCV and mixed where a high proportion of patients have HBV or HCV.*
- *The ethnicity of the population will have an impact on outcome in particular differences between European and Asian patients were highlighted.*
- *The mix of age and sex was similar between studies*
- *There are differences in the mix of fibrosis scores (Metavir). While this will not affect the AUROC score comparators it may be expected to influence the level of correlation between the index or comparator test and the reference.*
- *All of the examinations involved the right side of the liver. 10 ARFI and TE measurements were taken. The TE studies were rejected if reproducibility of scores did not meet the makers recommendations. There were no recommendation for ARFI but centres followed the same approach as with TE. The depth from which the ARFI examination was taken varied. The methodology of liver biopsy the reference test varied considerably. The quality of LB specimen varies between the studies but they were within the performance characteristics mandated by international guidelines [vi Rockey et al]*

7.4.3 Provide details of any subgroup analyses that were undertaken in the studies included in section 7.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

The subgroups in the study may be regarded as patients with HBV, HCV, HBV and C, NASH, Alcoholic Liver Disease. We have highlighted when subgroups were analysed or when a mixed patient group was involved.

7.4.4 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

Not relevant

7.4.5 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

Not relevant

7.5 Critical appraisal of relevant studies

Data were extracted on study details (study design, participant recruitment, setting, stated objective and clinical indication for testing relevant to this assessment for which data were reported), study participants (total number of participants and total number of HBV and HCV, study inclusion criteria, study exclusion criteria, participant age and gender distribution,) details of the index test, comparator(s) and reference standard (technical details of the test, details of who interpreted tests and how, threshold used to define a positive test) and study results.

All of the studies included in the review were diagnostic test accuracy (DTA) studies and the results extracted from these studies were unit of analysis (patient or lesion); AURUC value for different states of fibrosis (Metavir) score F0, F1..F4.

7.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables B7 and B8.

Table B7 Critical appraisal of randomised control trials

There were no randomised control trials and therefore a table summarising these studies is not included

Table B8 Critical appraisal of observational studies

Reference Number	2
Study name	Acoustic radiation force impulse-imaging in comparison to transient elastography for non-invasive assessment of liver fibrosis in chronic hepatitis C: A prospective international multicenter study
Cohort recruited	Prospective
Minimise bias?	n/a
Outcome minimise bias?	n/a
Identified confounding factors?	Yes
Accounted for confounding factors	Not stated
Follow-up	n/a
Precise CI y/n	Yes

Table B8 Critical appraisal of observational studies

Reference Number	25
Study name	Acoustic radiation force impulse imaging for non-invasive assessment of liver fibrosis in chronic hepatitis B
Cohort recruited	Prospective
Minimise bias?	n/a
Outcome minimise bias?	n/a
Identified confounding factors?	Yes - listed fibrosis F0 29%,F1 43%,F2 17%,F3 7%,F4 4%
Accounted for confounding factors	Not stated
Follow-up	n/a
Precise CI y/n	Yes

Table B8 Critical appraisal of observational studies

Reference Number	26
Study name	Acoustic Radiation Force Impulse Elastography for fibrosis evaluation in patients with chronic hepatitis C: An international multicenter study
Cohort recruited	Retrospective - multicentre
Minimise bias?	n/a
Outcome minimise bias?	n/a
Identified confounding factors?	Yes - listed fibrosis F0 6.7%,F1 26.4%,F2 22.1%,F3 20.4%,F4 24.4%
Accounted for confounding factors	Yes Asian vs European
Follow-up	n/a
Precise CI y/n	Yes

Table B8 Critical appraisal of observational studies

Reference Number	34
Study name	Comparative Study Concerning the Value of Acoustic Radiation Force Impulse Elastography (ARFI) in Comparison with Transient Elastography (TE) for the Assessment of Liver Fibrosis in Patients with Chronic Hepatitis B and C
Cohort recruited	Prospective with informed consent
Minimise bias?	n/a
Outcome minimise bias?	n/a
Identified confounding factors?	Yes - - listed fibrosis F0 13%,F1 40%,F2 19%,F3 9%,F4 19%
Accounted for confounding factors	Not stated
Follow-up	n/a
Precise CI y/n	Yes

Table B8 Critical appraisal of observational studies

Reference Number	44
Study name	Performance of Acoustic Radiation Force Impulse imaging for the staging of liver fibrosis: A pooled meta-analysis
Cohort recruited	Prospective and retrospective - Pooled meta analysis
Minimise bias?	n/a
Outcome minimise bias?	n/a
Identified confounding factors?	Yes - listed fibrosis F0 13%,F1 21%,F2 23%,F3 13%,F4 27%
Accounted for confounding factors	No
Follow-up	n/a
Precise CI y/n	No

Table B8 Critical appraisal of observational studies

Reference Number	45
Study name	Acoustic radiation force impulse imaging (ARFI) for non-invasive detection of liver fibrosis: Examination standards and evaluation of interlobe differences in healthy subjects and chronic liver disease
Cohort recruited	Prospective with informed consent
Minimise bias?	n/a
Outcome minimise bias?	n/a
Identified confounding factors?	Yes
Accounted for confounding factors	No
Follow-up	n/a
Precise CI y/n	No

Table B8 Critical appraisal of observational studies

Reference Number	47
Study name	Is it better to use two elastographic methods for liver fibrosis assessment?
Cohort recruited	Prospective with informed consent
Minimise bias?	n/a
Outcome minimise bias?	n/a
Identified confounding factors?	Yes - listed fibrosis F0 6.6%,F1 16.2%,F2 26.4%,F3 23.9%,F4 26.9%
Accounted for confounding factors	No
Follow-up	n/a
Precise CI y/n	Yes

Table B8 Critical appraisal of observational studies

Reference Number	52
Study name	Comparison of transient elastography (TE) and acoustic radiation force impulse (ARFI) for noninvasive staging of liver fibrosis in patients with chronic hepatitis C
Cohort recruited	
Minimise bias?	n/a
Outcome minimise bias?	n/a
Identified confounding factors?	Yes - listed fibrosis F0 9.4%,F1 28.0%,F2 23.7%,F3 17.3%,F4 21.6%
Accounted for confounding factors	No
Follow-up	n/a
Precise CI y/n	No

Table B8 Critical appraisal of observational studies

Reference Number	55
Study name	Which is the best noninvasive ultrasound method for the evaluation of liver fibrosis?
Cohort recruited	
Minimise bias?	n/a
Outcome minimise bias?	n/a
Identified confounding factors?	Yes
Accounted for confounding factors	No
Follow-up	n/a
Precise CI y/n	Yes

Table B8 Critical appraisal of observational studies

Reference Number	61
Study name	Performance of a new elastographic method (ARFI technology) compared to unidimensional transient elastography in the noninvasive assessment of chronic hepatitis C. Preliminary results
Cohort recruited	Prospective with informed consent
Minimise bias?	n/a
Outcome minimise bias?	n/a
Identified confounding factors?	Yes - listed fibrosis F0 12.5%,F1 26.6%,F2 16.1%,F3 7.1%,F4 37.5%
Accounted for confounding factors	selection bias -uneven distribution of fibrosis stages and overrepresentation of patients with severe fibrosis-cirrhosis
Follow-up	n/a
Precise CI y/n	Yes

Table B8 Critical appraisal of observational studies

Reference Number	48
Study name	How efficient is acoustic radiation force impulse elastography for the evaluation of liver stiffness?
Cohort recruited	Retrospective
Minimise bias?	n/a
Outcome minimise bias?	n/a
Identified confounding factors?	Yes - listed fibrosis F0 24%,F1 24%,F2 15%,F3 10%,F4 26%
Accounted for confounding factors	No
Follow-up	n/a
Precise CI y/n	Yes

7.6 Results of the relevant studies

7.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table B9.

7.6.2 Justify the inclusion of outcomes in table B9 from any analyses other than intention-to-treat.

For each outcome for each included study, provide the following information:

The primary hypothesis under consideration was in all cases comparison between ARFI and LB with TE as a comparator.

statistical analysis used for testing hypotheses. In some studies the correlation between the index and comparator test and the reference were calculated.

The sample size is given in table B8.

The outcome name and unit of measurement. The primary outcomes were either the correlation between the reference and the tests ARFI and TE or the AUROC score of these tests

The size of the effect.

A 95% confidence interval.

No patients withdrew. The patients who were excluded from the analysis are those where the qa of the index or comparator was not met as described earlier. In general this is the difference in the population and number of patients given for the study (Tables B2)

ARFI and TE are used in current clinical practice.

Although some papers describe themselves as interim these still stand alone as any future study will be the addition of patients. None of these studies mentioned when they would be 'closing the books'.

Table B9 Outcomes from published and unpublished studies

Reference Number	2
Study name	Acoustic radiation force impulse-imaging in comparison to transient elastography for non-invasive assessment of liver fibrosis in chronic hepatitis C: A prospective international multicenter study
ARFI Value	n/a
ARFI 95% CI	Not relevant
ARFI Type	n/a
ARFI p value	n/a
TE Value	n/a
TE 95% CI	Not relevant
TE Type	n/a
TE p value	n/a
ARFI F0	n/a
ARFI F1	0.75 (0.67-0.83)p=0.28
ARFI F2	0.81 (0.74-0.88) p=0.15
ARFI F3	0.88 (0.82-0.94)p=0.11
ARFI F4	0.89 (0.83-0.96)p=0.??
TE F0	n/a
TE F1	0.80 (0.72-0.88) p=0.28
TE F2	0.85 (0.8-0.91) p=0.15
TE F3	0.92 (0.89-0.97) p=0.11
TE F4	0.94 (0.90-0.98) p=0.19

Table B9 Outcomes from published and unpublished studies

Reference Number	25
Study name	Acoustic radiation force impulse imaging for non-invasive assessment of liver fibrosis in chronic hepatitis B
ARFI Value	r=0.415
ARFI 95% CI	Not relevant
ARFI Type	Spearman
ARFI p value	(p=0000019)
TE Value	r=0.556
TE 95% CI	Not relevant
TE Type	Spearman
TE p value	(p=0000000082)
ARFI F0	n/a
ARFI F1	0.66(0.55-0.78)
ARFI F2	0.73(0.61-0.85)
ARFI F3	0.94(0.88-0.997)
ARFI F4	0.97(0.93-1.0)
TE F0	n/a
TE F1	0.78(0.68-0.88)
TE F2	0.82(0.70-0.93)
TE F3	0.94(0.88-0.99)
TE F4	0.97 (0.86-1.0)

Table B9 Outcomes from published and unpublished studies

Reference Number	26
Study name	Acoustic Radiation Force Impulse Elastography for fibrosis evaluation in patients with chronic hepatitis C: An international multicenter study
ARFI Value	r = 0.654
ARFI 95% CI	Not relevant
ARFI Type	Spearman
ARFI p value	p < 0.0001
TE Value	n/a
TE 95% CI	Not relevant
TE Type	n/a
TE p value	n/a
ARFI F0	n/a
ARFI F1	0.78
ARFI F2	0.79
ARFI F3	0.83
ARFI F4	0.84
TE F0	n/a
TE F1	n/a
TE F2	n/a
TE F3	n/a
TE F4	n/a

Table B9 Outcomes from published and unpublished studies

Reference Number	34
Study name	Comparative Study Concerning the Value of Acoustic Radiation Force Impulse Elastography (ARFI) in Comparison with Transient Elastography (TE) for the Assessment of Liver Fibrosis in Patients with Chronic Hepatitis B and C
ARFI Value	C: r=0.490 B:r=0.356,
ARFI 95% CI	Not relevant
ARFI Type	Spearman
ARFI p value	C:p<.0001 B:p<.01
TE Value	C:r=0.660 B:r=0.403
TE 95% CI	Not relevant
TE Type	Spearman
TE p value	C:p<.0001 B:p=.004
ARFI F0	n/a
ARFI F1	n/a
ARFI F2	n/a
ARFI F3	n/a
ARFI F4	n/a
TE F0	n/a
TE F1	n/a
TE F2	n/a
TE F3	n/a
TE F4	n/a

Table B9 Outcomes from published and unpublished studies

Reference Number	44
Study name	Performance of Acoustic Radiation Force Impulse imaging for the staging of liver fibrosis: A pooled meta-analysis
ARFI Value	n/a
ARFI 95% CI	Not relevant
ARFI Type	n/a
ARFI p value	n/a
TE Value	n/a
TE 95% CI	Not relevant
TE Type	n/a
TE p value	n/a
ARFI F0	n/a
ARFI F1	n/a
ARFI F2	C: 0.88 (0.83, 0.93) B:0.79 (0.63, 0.96)
ARFI F3	C: 0.90 (0.84, 0.97)B:0.83 (0.70, 0.96)*
ARFI F4	C: 0.92 (0.87, 0.98)B:0.90 (0.79, 1.00)*
TE F0	n/a
TE F1	n/a
TE F2	n/a
TE F3	n/a
TE F4	n/a

Table B9 Outcomes from published and unpublished studies

Reference Number	45
Study name	Acoustic radiation force impulse imaging (ARFI) for non-invasive detection of liver fibrosis: Examination standards and evaluation of interlobe differences in healthy subjects and chronic liver disease
ARFI Value	r=.532 (LLL) r=.661 (RLL)
ARFI 95% CI	Not relevant
ARFI Type	n/a
ARFI p value	n/a
TE Value	n/a
TE 95% CI	Not relevant
TE Type	n/a
TE p value	n/a
ARFI F0	n/a
ARFI F1	n/a
ARFI F2	n/a
ARFI F3	n/a
ARFI F4	n/a
TE F0	n/a
TE F1	n/a
TE F2	n/a
TE F3	n/a
TE F4	n/a

Table B9 Outcomes from published and unpublished studies

Reference Number	47
Study name	Is it better to use two elastographic methods for liver fibrosis assessment?
ARFI Value	(r = 0.730)
ARFI 95% CI	Not relevant
ARFI Type	Spearman
ARFI p value	n/a
TE Value	(r = 0.741)
TE 95% CI	Not relevant
TE Type	Spearman
TE p value	n/a
ARFI F0	n/a
ARFI F1	n/a
ARFI F2	0.84
ARFI F3	n/a
ARFI F4	0.91
TE F0	n/a
TE F1	n/a
TE F2	0.87
TE F3	n/a
TE F4	0.97

Table B9 Outcomes from published and unpublished studies

Reference Number	52
Study name	Comparison of transient elastography (TE) and acoustic radiation force impulse (ARFI) for noninvasive staging of liver fibrosis in patients with chronic hepatitis C
ARFI Value	n/a
ARFI 95% CI	Not relevant
ARFI Type	n/a
ARFI p value	n/a
TE Value	n/a
TE 95% CI	Not relevant
TE Type	n/a
TE p value	n/a
ARFI F0	n/a
ARFI F1	n/a
ARFI F2	0.86
ARFI F3	0.94
ARFI F4	0.89
TE F0	n/a
TE F1	n/a
TE F2	0.78
TE F3	0.83
TE F4	0.80

Table B9 Outcomes from published and unpublished studies

55	55
Which is the best noninvasive ultrasound method for the evaluation of liver fibrosis?	Which is the best noninvasive ultrasound method for the evaluation of liver fibrosis?
r=0.469	r=0.469
Not relevant	Not relevant
n/a	n/a
p<0.0001	p<0.0001
n/a	n/a
Not relevant	Not relevant
n/a	n/a
n/a	n/a
n/a	n/a
n/a	n/a
0.65	0.65
n/a	n/a
0.87	0.87
n/a	n/a
n/a	n/a
0.73	0.73
n/a	n/a
0.94	0.94

Table B9 Outcomes from published and unpublished studies

Reference Number	61
Study name	Performance of a new elastographic method (ARFI technology) compared to unidimensional transient elastography in the noninvasive assessment of chronic hepatitis C. Preliminary results
ARFI Value	r=0.717
ARFI 95% CI	Not relevant
ARFI Type	n/a
ARFI p value	p<0.0001
TE Value	n/a
TE 95% CI	Not relevant
TE Type	n/a
TE p value	n/a
ARFI F0	n/a
ARFI F1	0.71
ARFI F2	0.85
ARFI F3	0.87
ARFI F4	0.91
TE F0	n/a
TE F1	0.90
TE F2	0.94
TE F3	0.93
TE F4	0.95

Table B9 Outcomes from published and unpublished studies

Reference Number	48
Study name	How efficient is acoustic radiation force impulse elastography for the evaluation of liver stiffness?
ARFI Value	r = 0.646
ARFI 95% CI	n/a
ARFI Type	Spearman
ARFI p value	P < 0.0001
TE Value	p=0.870
TE 95% CI	Not relevant
TE Type	Spearman
TE p value	P < 0.0001
ARFI F0	n/a
ARFI F1	n/a
ARFI F2	0.89
ARFI F3	n/a
ARFI F4	0.93
TE F0	n/a
TE F1	n/a
TE F2	0.95
TE F3	n/a
TE F4	0.99

7.7 Adverse events

In section 7.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

7.7.1 Using the previous instructions in sections 7.1 to 7.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

The Medline database was interrogated to understand any adverse events associated with the technique. The terms ARFI and Adverse were used. We found 8 studies but none of these was relevant.

7.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table B10.

Table B10 Adverse events across patient groups was not completed. There were no reports of adverse events using the ARFI software. Adverse events associated with liver biopsy are well described (ref).

Table B10 Adverse events across patient groups

7.7.3 Describe all adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude).

None recorded

7.7.4 Provide a brief overview of the safety of the technology in relation to the scope.

The ARFI technique uses additional software to an existing ultrasound instrument. No adverse effects were reported in any of the included studies and no additional evidence has been identified that indicates that ARFI is specifically associated with any adverse effects.

7.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 7.8 should be read in conjunction with the 'Medical Technologies Evaluation Programme Methods Guide', available from www.nice.org.uk/mt

When direct comparative evidence about two key treatments is not available, indirect treatment comparison methods can be used to derive comparative estimates of the effectiveness of these two treatments. For example, if there is evidence comparing A with B, and B with C, indirect treatment comparison techniques could be used to help compare A with C. This option should be considered even though it may be less suitable for the evaluation of many new medical technologies, either because of lack of multiple comparators in the evidence base, or limitations in the evidence base/study designs.

The evidence-based QUADAS tool was used for assessing the methodological quality of test accuracy studies. The areas reviewed were:-

- *index test*
- *comparator test*
- *reference standard*

No study reported data on patient preferences including those not reporting for the reference standard and therefore not entering the study, or reference standard associated adverse events.

The results of the studies included in this review were summarised by population (HBV, HCV, Other) and further stratified by comparator test(s) (TE, LB), as appropriate. For all included studies the AUROC results tables for index test, comparator and target condition was reported. In addition the correlation coefficient between the index test and comparator test and the reference standard is presented.

We identified two systematic reviews (DARE).

The meta analysis performed by Bota et al did not provide summary information in the format which was suitable for this analysis. Most importantly it failed to differentiate between the patient populations when summarising the accuracy data. [vii Bota et al]

The meta analysis performed by Nierhoff et al did differentiate between the patient populations when summarising the accuracy date. For the diagnosis of significant fibrosis (F≥2) the AUROC with the corresponding standard errors were available in 26 studies. They found the AUROC for the diagnosis of significant fibrosis 0.84, severe fibrosis was 0.89, and liver cirrhosis 0.91. They comment that the AUROC value for F≥3 is higher if only HCV patients are included. [viii Nierhoff et al] This is in line with our conclusions.

7.8.1 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

The population number in all of the studies was high. The methodology in all of the studies was similar excepting the liver biopsy. Understandably different centres have different means of sample collection dictated by the surgeon and histopathologist. We did not consider that this affected the comparison between sites but may account for the lower accuracy of either TE or ARFI in measuring elasticity in patients with low or no fibrosis.

The fibrosis score (Metavir) varied between studies. This is summarized in the table below along with the reported correlation coefficient. Studies with a higher proportion of patients classed as Metavir 1 had a lower correlation for ARFI or TE.

Table B11 Correlation between methods and patient mix

	Metavir Score					Correlation	
Study	F0	F1	F2	F3	F4	VTq	TE
47	6.6%	16.2%	26.4%	23.9%	26.9%	r=0.730	r = 0.741
26	6.7%	26.4%	22.1%	20.4%	24.4%	r=0.654	
44	13.0%	21.0%	23.0%	13.0%	27.0%		
52	9.4%	28.0%	23.7%	17.3%	21.6%		
61	12.5%	26.6%	16.1%	7.1%	37.5%	r=0.717	
48	24.0%	24.0%	15.0%	10.0%	26.0%	r=0.646	r=0.870
34	13.0%	40.0%	19.0%	9.0%	19.0%	r=0.490	r=0.66
xi	0.0%	68.0%	11.0%	11.0%	10.0%	r=0.764	
25	29.0%	43.0%	17.0%	7.0%	4.0%	r=0.415	r=0.556
45						r=0.661	
55						r=0.469	

The improved correlation between the Metavir score and VTq in patients with severe fibrosis may be a function of sampling and the fact that fibrosis is extensive while with F1 and F2 where the correlation is less precise this may be due to sampling error both in terms of elastography but more importantly liver biopsy.

10 studies assessed the diagnostic and prognostic accuracy of ARFI and TE in identifying moderate-to-severe fibrosis and cirrhosis in patients with Hepatitis B and/or Hepatitis C infection. 13 studies compared ARFI and TE but three did not provide AUROC scores only correlation coefficients.

Four studies either didn't differentiate between Hepatitis B and C in their analysis or included a limited number of patients where the etiology was other than Hepatitis B and Hepatitis C infection.

There were 6 studies which looked at Hepatitis C. The median AUROC value for F≥2 = 0.851 and F≥3 =0.88 and F4 0.91.

The two studies which reviewed hepatitis B the AURAC value for F≥2 exceeded 0.73 and F≥3 exceeded 0.83 and F4 exceeded 0.90.

There were 4 studies which looked at a mixed population but weighted towards HCV. The median AUROC value for F≥2 = 0.80 and F≥3 exceeded 0.85 and F4 0.88.

Table B12 AUROC VALUES FOR ARFI AND TE IN THE RELEVANT STUDIES

Study no	Population	ARFI (VTq)				TE (Fibroscan)			
		F1	F2	F3	F4	F1	F2	F3	F4
44	Hep B (n = 51)		0.79 (0.63, 0.96)	0.83 (0.70, 0.96)	0.90 (0.79, 1.00)				
25	Hep B (n=114)	0.66 (0.55-0.78)	0.73 (0.61-0.85)	0.94 (0.88-0.997)	0.97 (0.93-1.0)	0.78 (0.68-0.88)	0.82 (0.70-0.93)	0.94 (0.88-0.99)	0.97 (0.86-1.0)
52	Hep C (n=139)		0.86	0.94	0.89		0.78	0.83	0.8
61	Hep C (n=112)	0.709	**0.851**	0.869	0.911	**0.902**	0.941	0.926	**0.945**
57	Hep C (n=112)	**0.725**	0.869	0.9	0.936	0.918	0.961	0.957	0.97
47	Hep C (n = 197)		0.84		**0.91**		**0.87**		0.97
44	Hep C (n = 380)		0.88 (0.83, 0.93)	0.90 (0.84, 0.97)	0.92 (0.87, 0.98)				
2	Hep C (n=253)	0.75 (0.67-0.83)	0.81 (0.74-0.88)	**0.88 (0.82-0.94)**	0.89 (0.83-0.96)	0.80 (0.72-0.88)	0.85 (0.8-0.91)	**0.92 (0.89-0.97)**	0.94 (0.90-0.98)
26	Hep C (n=914)	0.779	0.792	0.829	0.842				
17	Hep B (n =65), Hep C (n = 83)		**0.8**	0.93	0.95		**0.81**	0.9	**0.92**
55	Hep B (N=17), Hep C (N=54)		0.649		0.868		0.731		0.936
21	Hep B, Hep C, Other (n=185)			0.85	**0.88**			0.89	0.91
48	Unclear (n=223)		0.89		0.931		0.953		0.985

Table B12 reviews the mean AUROC scores presented for the given etiologies. We have highlighted the median score (red) where there are sufficient studies of that patient population. We feel that a mean score would be inappropriate as the data is not normally distributed. A mean score would provide a higher AUROC number than presented.

The accuracy of the technique can be described by the AUROC value. A diagnostic tool is defined as being perfect if the area under the ROC curve (AUROC) is 100%, excellent if over 90%, and good over 80% (ix Swets 1988)

Identification of F3 and F4 for HBV and HCV by ARFI the median AUROC exceeds 0.8. Identification of =>F2 AUROC exceeds 0.8 in the case of HCV but the evidence base does not permit a figure for HBV.

Comparison between VTq and TE for HBV/HCV combined studies showed that the AUROC values in these studies were generally below those where

the populations had been evaluated separately. Moreover the correlation coefficient in these studies was lower than in those where the populations were evaluated separately.

A qualitative synthesis of the conclusions made in the studies reviewed is that ARFI and TE are equivalent in terms of the accuracy of the measurements made although there is some suggestion that TE may be marginally more accurate in identifying early fibrosis F1.

7.9 Interpretation of clinical evidence

7.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology.

Clinical benefit

ARFI can be used in clinical practice as a good diagnostic tool for the diagnosis of significant fibrosis (f2) and as an excellent tool for the diagnosis of severe fibrosis (f3) and liver cirrhosis (f4).

In chronic viral hepatitis, the knowledge of the stage of liver fibrosis is important for prognosis and for decisions about antiviral treatment.

Early detection of severe fibrosis (F3 or higher) is essential since patients are at:-

- *high risk of developing complications*
  - *portal hypertension*
  - *hepatocellular carcinoma (HCC)*
- *recommended for antiviral treatment*

Elastography measurements have a higher accuracy (AUROC) and better correlation with the stage of fibrosis as determined by the Metavir score as the extent of fibrosis increases.

The diagnostic accuracy of ARFI quantified by AUROC for Hepatitis B or C patients F≥F3 exceeded 0.80. The progression from stage 2 to stage 3 or

above is of most importance clinically as this transition marks the point at which patients are provided with antiviral therapy. Treatment of patients with severe fibrosis or cirrhosis have been regarded as those which offer benefit in terms of safety and cost.

A high proportion of patients ~97% are suitable for investigation. ARFI unlike TE is not influenced by the presence of ascites, inflammatory hepatitis or steatosis. Patient weight (BMI) is less of an influence with ARFI.

Diagnostic ultrasound is a necessary part in the triage of patients with hepatitis infection. ARFI unlike TE is a follow on exam from the b-mode procedure and can be used in conjunction with the findings of ultrasound imaging. ARFI can select the area of the liver using the region of interest (ROI) under B mode imaging.

A combination with serum fibrosis markers might further improve the diagnostic accuracy as has been reported for the combination of transient elastography and serum markers [x Vergniol et al 2011].

Adverse events

There were no adverse events reported using ARFI (or TE) but there are adverse events from liver biopsy but these weren't specifically reported.

7.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

Strengths

The studies are straightforward, easy to interpret and provided a quantitative answer. The results of these studies were in line with other studies (not analysed) which looked at the individual tests.

Limitations

Few papers on Hepatitis B and where studies are mixed (HBV and HCV) the majority of patients are HCV.

A limitation is that authors have not always presented both the correlation coefficient for the index, comparator vs the reference or AURAC scores for each Metavir score.

None of the studies were performed in the UK. Their assessment of ethnicity was restricted to Asian patients there was no comment regarding patients of other ethnicities excepting white European.

The fibrosis status of patients attending clinics in the UK is unclear

No comment was made on follow up of patients and whether tests including the reference test were consistent with later findings

There is some variation in the cut off values used between studies.

7.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and system-benefits described in the scope.

This study demonstrates that ARFI elastography is able to assess parenchymal stiffness of the liver with good correlation to degree of fibrosis and can be performed as part of a routine ultrasound study to aid in the assessment of liver fibrosis in patients with Hepatitis B or C thus optimising the patient pathway.

7.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

There are no patient groups which are unsuitable for the study.

Care needs to be taken in interpreting the results as the ethnic mix of patients is unclear. The best cut-off for predicting significant fibrosis (F ≥ 2) and for liver cirrhosis (F = 4) was significantly different between European and Asian patients resulting in a higher accuracy when diagnosing European populations. (26)

7.9.5 Based on external validity factors identified in 7.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

None

Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

8 Existing economic evaluations

8.1 Identification of studies

8.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10, appendix 3.

Search strategies were based on the target condition (hepatitis) the intervention (ARFI) and/or the comparator (Fibroscan) and Economic. The health technology assessments which looked at the cost of a TE examination and or liver biopsy in the assessment of fibrosis from any etiology were viewed as suitable source material.

8.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

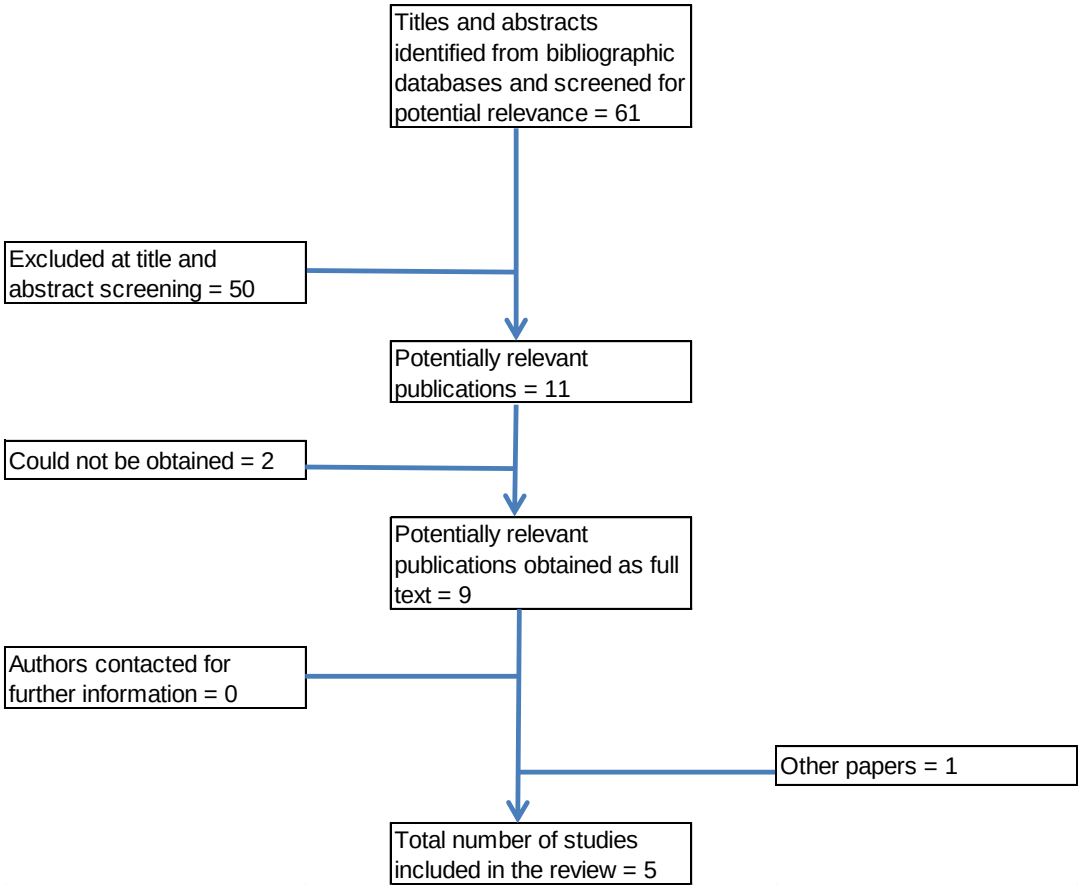
Table C1 Selection criteria used for health economic studies

Inclusion criteria	
Population	*Liver Fibrosis*
Interventions	*ARFI using VTq or Liver biopsy and/or FibroScan*
Outcomes (Primary)	*Cost of intervention*
Study design	*Economic Analysis*
Language restrictions	*Abstract in English*
Search dates	*2009- 2014 Present*
Exclusion criteria	
Population	*Undefined Liver Disease*
Interventions	*Test other than described above*
Outcomes	*Cost comparisons not provided*

Study design	*reviews, editorials, opinion pieces, case reports; studies reporting only technical aspects of the test; studies with < 10 participants*
Language restrictions	*No English Abstract*
Search dates	*N/a*

8.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Table C1 Prisma diagram



8.2 Description of identified studies

8.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table C2.

Table C2 Summary list of all evaluations involving costs

Study name (year)	**Location of study**	**Summary of model and comparators**	**Patient population *(key characteristics, average age)***	**Costs *(intervention and comparator)***	***Patient outcomes (clinical outcomes, utilities, life expectancy, time to recurrence for intervention and comparator)***	***Results (annual cost savings, annual savings per patient, incremental cost per QALY)***
CEP08053 (2009)	UK	TE vs LB	HBV,HCV,NASH, Alcoholic	£855.56 (LB) £18.68 (TE)	Diagnosis of significant fibrosis	£441 per patient
Stevenson et al (2012)	UK	TE vs LB	ALD	£894.00 (LB) £50.00 (TE)	Diagnosis of significant fibrosis	Insufficient evidence
Canavan (2013)	UK	TE vs LB	HCV	£528.00 (LB) £20.41 (TE)	Diagnosis of significant fibrosis	£6,557.06 per QALY
Whitty et al (2014)	AUS	TE vs LB	HCV	Unclear (LB) AU$49.00 (TE)	Diagnosis of significant fibrosis	AUD2,716
Steadmann et al (2013)	CAN	TE vs LB	HBV,HCV,NASH, Alcoholic	CAN461(LB) CAN99 (TE)	Diagnosis of significant fibrosis	CAN1,427 (HBV) CAN1,861 (HCV)

8.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table C3.

Table C3a Quality assessment of health economic studies

Study name:-Cost effectiveness of ultrasound elastography in the assessment of liver fibrosis		
Study design		
Study question		**Comments**
1. Was the research question stated?	yes	
2. Was the economic importance of the research question stated?	yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	yes	
5. Were the alternatives being compared clearly described?	yes	
6. Was the form of economic evaluation stated?	yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	yes	
8. Was/were the source(s) of effectiveness estimates used stated?	yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	yes	
12. Were the methods used to value health states and other benefits stated?	yes	
13. Were the details of the subjects from whom valuations were obtained given?	yes	
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question discussed?	yes	
16. Were quantities of resources reported separately from their unit cost?	yes	
17. Were the methods for the estimation of quantities and unit costs described?	yes	

18. Were currency and price data recorded?	yes	
19. Were details of price adjustments for inflation or currency conversion given?	yes	UK Study
20. Were details of any model used given?	yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	yes	
22. Was the time horizon of cost and benefits stated?	yes	
23. Was the discount rate stated?	yes	
24. Was the choice of rate justified?	yes	
25. Was an explanation given if cost or benefits were not discounted?	yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	yes	
27. Was the approach to sensitivity analysis described?	yes	
28. Was the choice of variables for sensitivity analysis justified?	yes	
29. Were the ranges over which the parameters were varied stated?	yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	yes	
31. Was an incremental analysis reported?	yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	yes	
33. Was the answer to the study question given?	yes	
34. Did conclusions follow from the data reported?	yes	
35. Were conclusions accompanied by the appropriate caveats?	yes	
36. Were generalisability issues addressed?	yes	

Table Cb Quality assessment of health economic studies

Study name:- Non-invasive diagnostic assessment tools for the detection of liver fibrosis in patients with suspected alcohol-related liver disease: a systematic review and economic evaluation		
Study design		
Study question		**Comments**
1. Was the research question stated?	yes	
2. Was the economic importance of the research question stated?	yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	yes	
5. Were the alternatives being compared clearly described?	yes	
6. Was the form of economic evaluation stated?	yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	yes	
8. Was/were the source(s) of effectiveness estimates used stated?	yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	yes	
12. Were the methods used to value health states and other benefits stated?	yes	
13. Were the details of the subjects from whom valuations were obtained given?	yes	
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question discussed?	no	
16. Were quantities of resources reported separately from their unit cost?	no	
17. Were the methods for the estimation of quantities and unit costs described?	yes	
18. Were currency and price data recorded?	yes	

19. Were details of price adjustments for inflation or currency conversion given?	yes	UK Study
20. Were details of any model used given?	yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	yes	
22. Was the time horizon of cost and benefits stated?	yes	
23. Was the discount rate stated?	yes	3.5%
24. Was the choice of rate justified?	yes	
25. Was an explanation given if cost or benefits were not discounted?	yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	yes	
27. Was the approach to sensitivity analysis described?	yes	
28. Was the choice of variables for sensitivity analysis justified?	yes	
29. Were the ranges over which the parameters were varied stated?	yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	yes	
31. Was an incremental analysis reported?	yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	yes	
33. Was the answer to the study question given?	yes	
34. Did conclusions follow from the data reported?	yes	
35. Were conclusions accompanied by the appropriate caveats?	yes	
36. Were generalisability issues addressed?	yes	

Table C3c Quality assessment of health economic studies

Study name:- Defining cirrhosis with Fibroscan for entry to hepatocellular carcinoma surveillance in chronic hepatitis C: A UK cost effectiveness analysis		
Study design		
Study question		**Comments**
1. Was the research question stated?	yes	
2. Was the economic importance of the research question stated?	yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	yes	
5. Were the alternatives being compared clearly described?	yes	
6. Was the form of economic evaluation stated?	yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	yes	
8. Was/were the source(s) of effectiveness estimates used stated?	No	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	yes	
12. Were the methods used to value health states and other benefits stated?	yes	
13. Were the details of the subjects from whom valuations were obtained given?	yes	
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question discussed?	no	
16. Were quantities of resources reported separately from their unit cost?	no	
17. Were the methods for the estimation of quantities and unit costs described?	no	
18. Were currency and price data recorded?	yes	
19. Were details of price adjustments for	yes	UK Study

inflation or currency conversion given?		
20. Were details of any model used given?	yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	yes	
22. Was the time horizon of cost and benefits stated?	yes	
23. Was the discount rate stated?	yes	3.5%
24. Was the choice of rate justified?	yes	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	yes	
27. Was the approach to sensitivity analysis described?	yes	
28. Was the choice of variables for sensitivity analysis justified?	yes	
29. Were the ranges over which the parameters were varied stated?	yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	yes	
31. Was an incremental analysis reported?	yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	yes	Cost per study
33. Was the answer to the study question given?	yes	
34. Did conclusions follow from the data reported?	yes	
35. Were conclusions accompanied by the appropriate caveats?	yes	
36. Were generalisability issues addressed?	yes	

Table C3d Quality assessment of health economic studies

Study name:- Cost and time savings from a rapid access model of care using transient elastography to screen and triage patients with chronic Hepatitis C infection		
Study design		
Study question		**Comments**
1. Was the research question stated?	yes	
2. Was the economic importance of the research question stated?	yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	yes	Public Health System
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	yes	
5. Were the alternatives being compared clearly described?	yes	
6. Was the form of economic evaluation stated?	yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	yes	Activity based
8. Was/were the source(s) of effectiveness estimates used stated?	n/a	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	yes	
15. Was the relevance of productivity changes to the study question discussed?	yes	
16. Were quantities of resources reported separately from their unit cost?	yes	
17. Were the methods for the estimation of quantities and unit costs described?	n/a	
18. Were currency and price data recorded?	yes	

19. Were details of price adjustments for inflation or currency conversion given?	No	Australian Study
20. Were details of any model used given?	No	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
22. Was the time horizon of cost and benefits stated?	No	
23. Was the discount rate stated?	yes	5%
24. Was the choice of rate justified?	yes	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	no	
27. Was the approach to sensitivity analysis described?	n/a	
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	No	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	yes	
34. Did conclusions follow from the data reported?	yes	
35. Were conclusions accompanied by the appropriate caveats?	yes	
36. Were generalisability issues addressed?	yes	

Table C3e Quality assessment of health economic studies

Study name:- A health technology assessment of transient elastography in adult liver disease		
Study design		
Study question		**Comments**
1. Was the research question stated?	yes	
2. Was the economic importance of the research question stated?	yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	yes	Health care payer
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	yes	
5. Were the alternatives being compared clearly described?	yes	
6. Was the form of economic evaluation stated?	yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	yes	
8. Was/were the source(s) of effectiveness estimates used stated?	yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	yes	
12. Were the methods used to value health states and other benefits stated?	yes	
13. Were the details of the subjects from whom valuations were obtained given?	yes	
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question discussed?	yes	
16. Were quantities of resources reported separately from their unit cost?	yes	
17. Were the methods for the estimation of quantities and unit costs described?	yes	
18. Were currency and price data recorded?	yes	
19. Were details of price adjustments for	yes	Canadian study 2010 Can$

inflation or currency conversion given?		
20. Were details of any model used given?	yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	yes	
22. Was the time horizon of cost and benefits stated?	yes	
23. Was the discount rate stated?	no	No discounting due to short time course
24. Was the choice of rate justified?	no	
25. Was an explanation given if cost or benefits were not discounted?	yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	yes	
27. Was the approach to sensitivity analysis described?	yes	
28. Was the choice of variables for sensitivity analysis justified?	yes	
29. Were the ranges over which the parameters were varied stated?	yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	yes	
31. Was an incremental analysis reported?	yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	yes	
33. Was the answer to the study question given?	yes	
34. Did conclusions follow from the data reported?	yes	
35. Were conclusions accompanied by the appropriate caveats?	yes	
36. Were generalisability issues addressed?	yes	

9 De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.

The de novo cost analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

9.1 Description of the de novo cost analysis

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

Insufficient published evidence of the cost of using VTq.

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

Patients suffering from chronic Hepatitis B or C. The patients are those attending a clinic subsequent to diagnosis of chronic hepatitis infection. These patients will be expected to receive a liver biopsy on their first attendance and then they will be followed up at regular intervals and may receive subsequent biopsies. In the analysis we have assumed the group which we are reviewing is those who first present with chronic hepatitis.

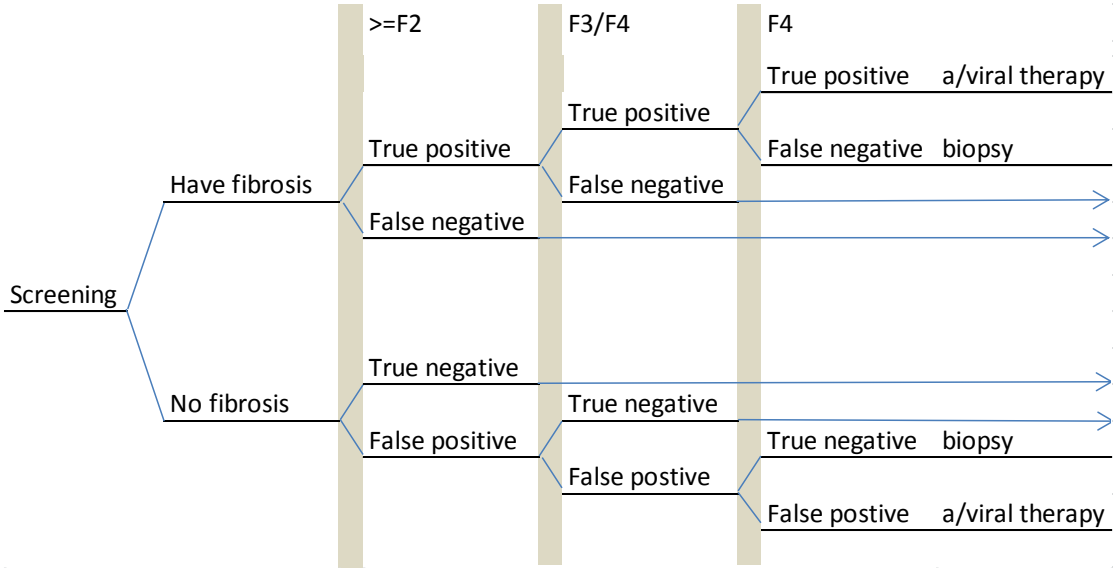
Technology and comparator

9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

The comparators are Liver Biopsy and Transient Elastography (Fibroscan) as detailed in the scope.

Model structure

9.1.4 Provide a diagram of the model structure you have chosen.



9.1.5 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

The patients screened are those referred by the GP – we assume a cohort of 1,000 HBV or HCV patients the fibrosis state of which is unknown. The sensitivity and specificity of the screening tests will show either positive results or negative results.

The sensitivity of elastography, alongside that of biopsy, will determine the number of patients who have cirrhosis who are not appropriately diagnosed.

The specificity of elastography will determine the number of patients who may receive unnecessary biopsy or, if a triaging strategy is not pursued, the number of patients who are monitored unnecessarily. The advantage of elastography is that fewer biopsies will be performed than in assumed current practice, which will be associated with reduced costs, and also reduced mortality and morbidity.

The estimated sensitivity and specificity for VTq is given in Tables C17a-c. No formal meta-analysis has been undertaken because of the potential heterogeneity within the trials in terms of the length of and the number of

portal tracts examined within the liver biopsy, the number of days between the test and performing the biopsy, the mixed populations and the different cut-off thresholds for diagnosing cirrhosis/fibrosis.

In order to provide an estimation of the cost-effectiveness of VTq, three scenarios for sensitivity and specificity are evaluated, which we have selected for classification of Metavir state (Table C15 a-c).

The prevalence of patients whom a secondary care clinician would want to biopsy is needed to determine the absolute number of TPs, FPs, TNs and FNs. The prevalence of fibrosis >=F2, >=F3 and F4 (Cirrhosis) has been difficult to estimate.

Prof. Paul Sidhu at Kings estimated that >=F2 was 15%.

Stevenson et al 2012 based on unreferenced clinical evidence took the value for patients presenting with Cirrhosis (F4) as 35%.

9.1.6 Provide a list of all assumptions in the cost model and a justification for each assumption.

Sensitivity and Specificity are taken from the literature searched. The range of sensitivity and specificity used is that highlighted in the various papers.

Sensitivity and specificity are correlated as they depend on the chosen cut-off values. We have not estimated sensitivity and specificity for all possible cut-off levels using a random effect estimator. We have taken the median and 25th percentile value (worst case) for sensitivity and specificity from the papers in which they were stated. We have taken the best case from papers in which the VTq measurement was made at least 2cm below the liver capsule.

Incidence of patients with Metavir scores of >=3 and >=2 who are seen in typical UK settings. The basis of these assumptions is personal input from our clinical advisors.

The cost of liver biopsy is taken from data presented by the NHS. The cost of the procedure is the base cost and the variation the market factor applied depending on the region in which the exam is performed.

No NHS data was found for the TE (Fibroscan) procedure cost. The CEP report (08053 2009) identified the cost of performing this examination on 5,000 patients pa as £18.68 in 2009 (Corrected for inflation £22.91 in 2014).

The only consumable cost associated with the elastography techniques is the cost of ultrasound gel. We have assumed the storage costs of the results to be negligible. The other cost is the per square metre cost for rent, utilities and departmental over heads. The maximum space required for the ultrasound exam is 4sqm.

The VTq examination will be subsequent to the diagnostic ultrasound examination and therefore that the additional cost will be based on the additional time taken to carry out the follow on examination. This NHS pricing structure is likely to view this study as an additional procedure. In 2013/14 the price for RA23Z Ultrasound Scan less than 20 minutes was £45 and for RA24Z Ultrasound Scan more than 20 minutes was £57. In the analysis for simplicity we have assumed VTq to be a stand-alone exam which will inflate the cost of the study.

We have not modelled individual aspects of the cost data. The price of the equipment is the list price and any variation would be towards a lower purchase price. We believe that both of the pieces of equipment under review are covered by an NHS Purchasing Framework Agreement.

The cost of the operator will vary depending on whether the member of staff is clinical or technical and the staffing grade. We discuss this later.

9.1.7 Define what the model's health states are intended to capture.

Triage patients such that those with with severe fibrosis or cirrhosis, are distinguished from those with no fibrosis or a milder condition.

9.1.8 Describe any key features of the cost model not previously reported. A suggested format is presented below.

Table C4 Key features of model not previously reported

The model is from the perspective of the payer (NHS). The costs and outcomes were not discounted as the model did not continue after screening. Patients who were subsequently screened after their initial screening were viewed as entering the algorithm as a new patient.

9.2 Clinical parameters and variables

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

The clinical evidence (AUROC) describes the accuracy of the method. The clinical evidence was consistent in showing that as the severity of fibrosis increases so the accuracy of both VTq and TE examinations increased. A number of the papers reviewed in part B also summarise the sensitivity and specificity of the methods. For VTq studies additionally we have added sensitivities and specificities from papers in which the method was compared with LB but without the comparator TE.

We have taken the median and 25th percentile value (worst case) for sensitivity and specificity from the papers in which they were stated. We have taken the best case from papers in which the VTq measurement was made at least 2cm below the liver capsule.

We have used a value for sensitivity and specificity for TE from the meta analysis of Steadmann et al 2013 and have taken the best and worst case from the confidence intervals obtained there in.

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

We have not extrapolated costs and outcomes beyond the study. It would be expected that the patients who were wrongly diagnosed using VTq i.e. those who were false positives would only receive a course of treatment and would be followed up using the method. The false negatives (those under the lowest threshold) would be expected to be reevaluated after 12 months.

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

We have viewed the outcome as one but various authors have used the evidence differently. This also affects their choice of cut off values. Some have simply used the method to rule Cirrhosis in or out. The elastography tests are three separate analysis of the same data and where the prevalence should reflect the analysis being performed.

9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Yes we have included Biopsy as the only intervention with associated adverse events. It has been assumed that elastography has no adverse events, aside from a potential misdiagnosis of cirrhosis. Biopsy, however, owing to its invasive nature, is associated with both mortality and morbidity. From the systematic review undertaken in this study, we have assumed that percutaneous biopsy has a probability of 0.09% of causing mortality, with an additional risk of causing a serious adverse event of 0.72%. (Stevenson et al 2012)

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Name: Professor Paul Sidhu Job Title: Consultant radiologist Employer: Kings College Hospital London Email address: paulsidhu@nhs.net Name: Dr Philip Shorvon Job Title: Consultant Radiologist Employer: Central Middlesex Hospital Email address: p.shorvon@nhs.net

Name: Professor William Rosenberg Job Title: Peter Scheuer Chair of Liver Disease Employer: Royal Free Hospital Email address: w.rosenberg@ucl.ac.uk

Name: Dr Peter Hayes Job Title: Professor of Hepatology Employer: NHS Lothian Email address: c/o Paul.Allan@nhslothian.scot.nhs.uk

Name: Dr. P.L. Allan Job Title: Director of Imaging NHS Lothian Employer: NHS Lothian Email address: Paul.Allan@nhslothian.scot.nhs.uk

- *the criteria for selecting the experts:-*
  - *Familiarity with the method VTq and Fibroscan*
- *the number of experts approached:- 4*
- *the number of experts who participated:- 4*
- *declaration of potential conflict(s) of interest:-*
  - *None declared excepting their potential assessment role with NICE*
- *the background information provided and its consistency with the totality of the evidence provided in the submission*
  - *We supplied a draft copy of the completed document. We provided a 'questionnaire' which highlighted what we believed to be the key points within the document.*
- *the method(s) used to collect and collate the opinions*
  - *We provided a 'questionnaire' which highlighted what we believed to be the key points within the document.*
- *the medium used to collect opinions:- self-administered questionnaire*
  - *E-mail response to the submitted questions*
- *the questions asked*
  - *See Appendix 5*

- *whether iteration was used in the collation of opinions: No*
- *the uncertainly around these values should be addressed in the sensitivity analysis.*

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table C5 below.

Table C5 Summary of variables applied in the cost model

Variable	**Value**	**Range or 95% CI (distribution)**	**Source**
Sensitivity	*0.90*	*see note*	Table C15
Specificity	*0.80*	*see note*	Table C15
Incidence	15%	*10%,15%,30%*	Clinical input
Throughput	*2,000*	*500-4,000*	Clinical input
Cost	*£15.02*	*None*	*Table C11*
CI, confidence interval			

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

The procedures are currently costed as follows. Liver biopsy has a series of tariffs depending on the intervention. We understand that in almost all cases biopsy is performed percutaneously (OPCS J14.1)

2013-14 tariff - admitted patient care & outpatient procedures

OPCS Code	***Code Description***	***Root HRG***	***HRG Root Description***	***HRG 1***	***Combined day case/ ordinary elective spell tariff (£)***	***with CC***	***Combinedday case/ ordinary elective spell tariff(£)***
J14.1	*Biopsy of liver NEC*	*GB04*	*Endoscopic/Radiology category 1*	*GB04Z*	*535*		
J171	*Endoscopic ultrasound examination of liver and biopsy of lesion of liver*	*GB02*	*Endoscopic/Radiology category 3*	*GB02C*	*973*	*GB02B*	*1,281*

2013-14 tariff - outpatient attendances

			Consultant-led tariff		
Treatment function	***Treatment function name***	***WF01B*** *First Attendance - Single Professional*	***WF02B*** *First Attendance - Multi Professional*	***WF01A*** *Follow Up Attendance - Single Professional*	***WF02A*** *Follow Up Attendance - Multi Professional*
301	*Gastroenterology*	*181*	*237*	*103*	*204*
306	*Hepatology*	*181*	*237*	*103*	*204*

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

Ultrasound elastography of liver

The OPCS-4.6 codes for Ultrasound Elastography are:

U36.4 Ultrasound elastography

Y98.- Radiology procedures

Z30.1 Liver

All codes must be present and sequenced in the order shown.

Codes from category Y98 will be assigned immediately after U36.4 Ultrasound elastography to identify the duration of the ultrasound. Fourth character assignment will depend on the duration of the procedure. When the duration is not known then the default code is Y98.1 Radiology of one body area (or < 20 minutes).

At present, it is not possible to distinguish between ultrasound elastography of liver using Fibroscan and ultrasound elastography of liver using Acoustic Radiation Forced Impulse imaging using OPCS-4.6 codes.

Ultrasound procedures are only coded when performed in an outpatient setting or in an inpatient setting when the patient has been admitted solely for the ultrasound. Therefore, if an ultrasound elastography is performed during an inpatient admission, unless the patient was admitted solely for that procedure, it would not be coded.

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

We have searched https://www.gov.uk/government/publications/payment-by-results-pbr-operational-guidance-and-tariffs 07_-_Tariff_information_spreadsheet_2013-14_v6.xls

The tariff received by the provider is multiplied by a nationally determined market forces factor (MFF). This is unique to each provider and reflects the fact that it is more expensive to provide services in some parts of the country than in others. The MFF takes into consideration staffing costs, buildings, land etc. On average, the MFF adds about 8% to the value of the tariff. In the South East the factor is over 10% and over 25% in London. (Source: A simple guide to Payment by Results).

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[1].

- *the criteria for selecting the experts:-*
  - *Familiarity with the method VTq and Fibroscan*
- *the number of experts approached:- 4*
- *the number of experts who participated:- 4*
- *declaration of potential conflict(s) of interest:-*
  - *None declared excepting their potential assessment role with NICE*
- *the background information provided and its consistency with the totality of the evidence provided in the submission*
  - *We supplied a draft copy of the completed document. We provided a 'questionnaire' which highlighted what we believed to be the key points within the document.*
- *the method(s) used to collect and collate the opinions*

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

  - *We provided a 'questionnaire' which highlighted what we believed to be the key points within the document.*
- *the medium used to collect opinions:- self-administered questionnaire*
  - *E-mail response to the submitted questions*
- *the questions asked*
  - *See Appendix 5*
- *whether iteration was used in the collation of opinions: No*
- *the uncertainly around these values should be addressed in the sensitivity analysis.*

Technology and comparators' costs

9.3.5 Provide the list price for the technology.

All prices exclude VAT

Acuson S2000 US System £59,700, VTq Software £4,415 with annual maintenance costs (yr 2) of £2,246

The capital equipment cost for a Fibroscan is £79,950 based on the standard 'M' series probe covering patients with a BMI <30, and including the XL probe for patients with a BMI >30 with annual maintenance costs (yr 2) of £4,500. (University of Leicester Hospitals Trust 2012).

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

We have used the list price of the Fibroscan Unit and of the Acuson S2000 plus VTq. We have calculated the costs of operating these units based on throughput. We have assumed that the Fibroscan cost on the number of patients examined and the time interval over which it is written off. For VTq we assume that the s2000 unit is used on a sessional basis and that therefore its cost will always be recovered and is therefore less dependent on the number of fibrosis patients which need to be scanned. In both cases we assume that the unit will also be used to scan patients where fibrosis derives from conditions other than HBV and HCV.

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model. A suggested format is provided in tables C6 and C7. Table C7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology.

In calculating the cost of the VTq examination we have assumed that up to ten patients can be examined in a session and therefore we have assumed that for every ten patients a centre sees this will require one session. We have assumed that the ultrasound equipment is used in ten sessions per week (i.e. fully used). The TE equipment can only be amortised over the fibrosis

patients. We have assumed that a part time staff member 0.5WTE will be oversee the unit in a lower throughput scenario (<2000 patients pa) and a full time member at higher throughputs.

VTq and Fibroscan deliver quantitative results and therefore we assume do not require specialist review prior to them being forwarded for clinical appreciation (cf lab tests).

Either Fibroscan or VTq can be costed using the PbR rates below.

RA23Z	*Ultrasound Scan less than 20 minutes*	*£45*
RA24Z	*Ultrasound Scan more than 20 minutes*	*£57*

The costs of an appointment has been identified as:

306 Hepatology £181 First appointment £103 subsequent appointment

These costs are not factored into any of equations as we expect a radiographer or nurse to use the equipment. If the equipment is used by a hepatologist and the time taken is ten minutes then this should be considered but we believe that in some analyses this cost is seen as 'free good'.

Table C6 Costs per treatment/patient associated with the technology in the cost model

Items	Value	Source
Price of the technology per treatment/patient	*£15.02*	*Appendix 5*
Consumables (if applicable)	*included*	*Appendix 5*
Maintenance cost	*included*	*Appendix 5*
Training cost	*included*	*Appendix 5*
Other costs	*included*	*Appendix 5*
Total cost per treatment/patient	*£15.02*	*1000+ patients pa*

Table C7 Costs per treatment/patient associated with the comparator technology in the cost model

Items	Value	Source
Cost of the Liver Biopsy per treatment/patient	*£615*	(GB04Z) NHS PbR
Consumables (if applicable)	*included*	
Maintenance cost	*included*	
Training cost	*included*	
Other costs	*included*	
Total cost per treatment/patient	*£569*	

Table C7a Costs per treatment/patient associated with the comparator technology in the cost model

Items	Value	Source
Cost of the Fibroscan per treatment/patient	*£25.33*	*Appendix 5*
Consumables (if applicable)	*included*	*Appendix 5*
Maintenance cost	*included*	*Appendix 5*
Training cost	*included*	*Appendix 5*
Other costs	*included*	*Appendix 5*

Total cost per treatment/patient	*£25.33*	*2500 patient pa*

Health-state costs

9.3.8 If the cost model presents health states, the costs related to each health state should be presented in table C8. The health states should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

Table C8 List of health states and associated costs in the economic model

Not relevant and therefore not included

Adverse-event costs

Complete table C9 with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

There we no adverse events when using VTq or Fibroscan elastography.

A serious adverse event associated with biopsy will result in a hospital stay. This has been assumed to cost £1000 by Stevenson and colleagues. For all patients who die as a result of biopsy, the costs of the biopsy are assumed to be incurred. The cost of these adverse events is estimated at £7 and this sum has been amortised over the cohort and added to the cost of each liver biopsy study. This approach was followed in (Stevenson et al 2012).

9.3.9

Table C9 List of adverse events and summary of costs included in the cost model

Adverse events	Items	Value	Reference
Biopsy	Total	£7.00 per biopsy	Stevenson 2012

Miscellaneous costs

9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

VTq cannot be used in ~3% of patients while TE is unusable in >7% of patients. We can assume that of the cohort (1000 patients) therefore only 970 patients received ultrasound and 30 of these patients received biopsy reducing the savings made. Likewise the figure for Fibroscan is 930 patients and 70 patients respectively. There is a net saving of £22,760 using VTq vs Fibroscan assuming all of the patients (1000) would otherwise have received a biopsy.

9.3.11 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

We have assumed that liver biopsy is a 'gold standard' while in fact as we have noted earlier it is imprecise. Misdiagnosis from biopsy will result in higher costs.

We have assumed that biopsy is undertaken on all patients identified as suffering from chronic hepatitis infection. A subset of these patients may well not receive a liver biopsy and may go on to develop cirrhosis with resultant cost.

We do not have data to quantify either of these opportunities

9.4 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

One way sensitivity analysis to test the robustness of the results with varying diagnostic accuracy (sensitivity and specificity), prevalence and cost. We have modelled costs based on patient throughput. We have assumed that the ultrasound unit is used elsewhere and that therefore the cost is per session and that the maximum patient number which can be reviewed in a sessionis is 10.

9.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

A deterministic sensitivity analysis was performed with best, worst and likely case scenarios presented.

We assume that the unit may be used to examine patients with other causes of fibrotic disease as well as HBV and HCV.

A probabilistic sensitivity analysis was not performed as sensitivity and specificity are not independent variables while costs are either published NHS PbR or are governed by National Framework agreements.

Complete table C10.1, C10.2 and/or C10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Table C10.1 Variables used in one-way scenario-based deterministic sensitivity analysis

Variable	Base-case value	Range of values
Sensitivity	*90%*	*80%-95%*
Specificity	*90%*	*80%-95%*
Prevalence	*15%*	*15%-45%*
Throughput	*1,000*	*500-2,500*

Table C10.2 Variables used in multi-way scenario-based sensitivity analysis

Variable	***Sensitivity***	***Specificity***	***Prevalence***
Base case	*Table C 15*	*Table C 15*	*10%*
Median Case	*Table C 15*	*Table C 15*	*15%*
Worst Case	*Table C 15*	*Table C 15*	*30%*

Table C10.3 Variable values used in probabilistic sensitivity analysis

Variable	Base-case value	Distribution

9.4.3 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

There is very little variation in the cost of operating the VTq unit. We have priced the cost per session and have assumed that within a session between five and ten patients will be scanned. The cost of a session is therefore between £15.02 and £30.05. We have assumed that the VTq procedure is a

stand alone procedure and is not additional to the diagnostic ultrasound scan. If this is the case the cost of the procedure will be much lower.

The procedure follows on from a diagnostic ultrasound examination which the NHS costs (delta) as £12 alternatively it could be viewed as an additional examination £45.

The Fibroscan unit can only be used to assess fibrosis. We have assumed a mean throughput of 2,500 (£25.33) with low throughputs of 1000 patients (£40.65) and high throughputs of 4,000 patients (£15.83). Its cost is therefore £45 based on published tariffs. The cost of the unit has been amortised over its lifespan and annual patient throughputs estimated. We have assumed an NHS cost of £45 the cost of a single ultrasound examination. In the document CEP08053 (2009) the cost of Fibroscan was estimated at £18.68 (Corrected for inflation £22.91 in 2014).

The staff cost is the most significant cost in performing an examination with either unit. We have assumed that the unit will be operated by a suitably trained nurse (grade 5/6) rather than a consultant physician (hepatologist). Likewise while a VTq exam could be performed by either a clinician (radiologist or physician) we has assumed that it will be operated by a Radiographer (Grade 7). For both the nurse and radiographer we took the median point in the band. The salaries were inflated to take account of pension and NI costs to the employer.

9.5 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base-case analysis

9.5.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in table C11.

In the table below costs are: VTq per session, Fibroscan annual.

Table C11 Base-case results

	VTq		Fibroscan	
Capital	£	1,904.15	£	16,218.43
Consumables	£	-	£	-
Staffing	£	5,427.48	£	45,365.56
Department	£	179.70	£	1,750.00

Both year 2. Lifespan VTq 5 years Fibroscan 7 years, VTq costs per session Fibroscan costs pa

Sessions per week	VTq		Fibroscan		WTE (Fibrosca	Patients
1	£	30.05	£	162.60	0.5	250
1	£	15.02	£	81.30	0.5	500
2	£	15.02	£	40.65	0.5	1000
3	£	15.02	£	27.10	0.5	1500
4	£	15.02	£	31.67	1	2000
5	£	15.02	£	25.33	1	2500
6	£	15.02	£	21.11	1	3000
7	£	15.02	£	18.10	1	3500
8	£	15.02	£	15.83	1	4000

Fibroscan low throughput scenario half time staff.

A detailed breakdown of how these figures were calculated is given in the accompanying spreadsheet.

9.5.2 Report the total difference in costs between the technology and comparator(s).

The VTq unit can be operated on a sessional basis and therefore the cost is the same for most throughput scenarios.

The Fibroscan is used solely for the purpose of estimating fibrosis. The unit cost varies from £40.65 at low throughputs (1000 pa) to £15.83 at high throughputs (4000 pa). Typical workload at UK hospitals is unclear. There is evidence which points to the lower rather than the higher figure being typical.

- *Hospital unveils new Fibroscan. Dr Sulleman Moreea estimated that they would scan ~20 patients per week (1000 patients per year). Bradford Teaching Hospitals January 15, 2014*
- *Armstrong et al 2012 Postgrad Med J doi:10.1136/postgradmedj-2012-131640 78 Patients per month*
- *Dr Philip Shorvon (Central Middx Hospital) personal communication ~1000 patients per year receive ARFI*

The cost of the liver biopsy is the published 2014 PbR value. This cost is the base value and takes into account the average MFF factor (8%).

9.5.3 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table C12.

Table C12 Summary of costs by category of cost per patient

Item	Cost *VTq*	Cost *Fibroscan*	Increment	Absolute increment	% absolute increment
Technology	*£3.81*	*£6.49*	*-£2.68*	*-£2,680*	*26%*
Consumable	*£0*	*£0*	*£0*	*£0*	*0%*
Staff cost	*£ 10.85*	*£18.17*	*-£7.32*	*-£7,320*	*71%*
Dept cost	*£ 0.36*	*£ 0.70*	*-£0.34*	*-£340*	*3%*
Total	*£15.02*	*£25.33*	*-£10.31*	*-£10,310*	*100%*
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					
Item	**Cost *VTq***	**Cost *Biopsy***	**Increment**	**Absolute increment**	**% absolute increment**
Technology	*£3.81*	*£0*	*£0*	*£0*	*0%*
Consumable	*£0*	*£0*	*£0*	*£0*	*0%*
Staff cost	*£ 10.85*	*£0*	*£0*	*£0*	*0%*
Dept cost	*£ 0.36*	*£0*	*£0*	*£0*	*0%*
Total	*£15.02*	*£615*	*-£599.08*	*-£599,080*	*100%*
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

The per patient cost of both VTq and Fibroscan will be increased by the failure rate of the techniques VTq 3% Fibroscan 7% if these studies then need to be repeated by liver biopsy. Costs based on 2,500 patients scanned.

9.5.4 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table C13.

Table C13 Summary of costs by health state per patient

Not appropriate

9.5.5 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table C14.

Table C14 Summary of costs by adverse events per patient

Not appropriate

Sensitivity analysis results

9.5.6 Present results of deterministic one-way sensitivity analysis of the variables described in table C10.1.

The intended purpose of the first evaluation is to exclude patients without fibrosis, The cut-off value should be chosen to maximise specificity (i.e. the proportion of people who genuinely do not have fibrosis who are correctly identified by VTq (or TE)), to reduce the risk of patients who do not have fibrosis undergoing costly liver biopsy.

Patients below the cut off value are regarded as negative. The negative predictive value is 97.84

Patients above the cut off value are regarded as positive. The positive predictive value is 44.32 and therefore these patients need to be reassessed. Both median and best case for >=F2 have less than 5% false negatives. The false negatives contain patients with fibrosis F0-F3. These patients will be reassessed at a future appointment. Development of fibrosis is slow and therefore this should not present a risk to the patient.

The intended purpose of the subsequent evaluation is to select patients with fibrosis. The cut-off value should be chosen that maximises sensitivity (i.e. the proportion of patients who genuinely have fibrosis who are correctly identified by VTq (or TE)), as this will minimise the risk of patients with severe fibrosis being mistakenly identified as not having the condition, and therefore not receiving the appropriate treatment.

The extent of fibrosis of the negative patients is unclear excepting it is unlikely that they have cirrhosis as this would also be evident on the diagnostic ultrasound image. Therefore this group of false negative patients (84 patients) will need a biopsy?

The false positive patients (8) will be treated with antiviral drugs even though this may be unnecessary. The cost of treatment with peginterferon alfa-2a plus ribavirin (Copegus) is estimated to be £3,215 for 16 weeks or £4,824 for 24 weeks of therapy (for people with genotypes 2 or 3), or £11,425 for 48 weeks of therapy (for people with genotypes 1 or 4). NICE technology appraisals [TA200] (2010).

Table C15a Summary patient pathway Incidence 10%

Patient numbers	Incidence		Incidence		Incidence	
1000	10%		10%		10%	
	Median		Best Case		Worst Case	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
F2-F4	78.75	82.20	90.20	80.00	75.00	76.15
True negatives	74%		72%		69%	
True positives	8%		9%		8%	
False positives	16%		18%		21%	
False negatives	2%		1%		3%	
Total	100%		100%		100%	
Accuracy	77%		82%		76%	
Positives	**239**		**270**		**290**	

	Incidence		Incidence		Incidence	
	33%		33%		26%	
	Median		Best Case		Worst Case	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
F3-F4	85.30	86.00	91.57	87.37	80.89	85.50
True negatives	77%		79%		77%	
True positives	9%		9%		8%	
False positives	13%		11%		13%	
False negatives	1%		1%		2%	
Total	100%		100%		100%	
Accuracy	86%		89%		85%	
Positives	**50**		**55**		**61**	

	Incidence		Incidence		Incidence	
	33%		45%		38%	
	Median		Best Case		Worst Case	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
F4	90.50	89.35	93.85	91.08	87.50	86.53
True negatives	80%		82%		78%	
True positives	9%		9%		9%	
False positives	10%		8%		12%	
False negatives	1%		1%		1%	
Total	100%		100%		100%	
Accuracy	90%		92%		87%	
Patients to biopsy	**41**		**46**		**48**	

Table C15b Summary patient pathway Incidence 15%

Patient numbers	Incidence		Incidence		Incidence	
1000	15%		15%		15%	
	Median		Best Case		Worst Case	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
F2-F4	78.75	82.20	90.20	80.00	75.00	76.15
True negatives	70%		68%		65%	
True positives	12%		14%		11%	
False positives	15%		17%		20%	
False negatives	3%		1%		4%	
Total	100%		100%		100%	
Accuracy	81%		83%		76%	
Positives	**269**		**305**		**315**	

	Incidence		Incidence		Incidence	
	44%		44%		36%	
	Median		Best Case		Worst Case	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
F3-F4	85.30	86.00	91.57	87.37	80.89	85.50
True negatives	73%		74%		73%	
True positives	13%		14%		12%	
False positives	12%		11%		12%	
False negatives	2%		1%		3%	
Total	100%		100%		100%	
Accuracy	85%		90%		85%	
Positives	**67**		**75**		**77**	

	Incidence		Incidence		Incidence	
-	44%		56%		50%	
	Median		Best Case		Worst Case	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
F4	90.50	89.35	93.85	91.08	87.50	86.53
True negatives	76%		77%		74%	
True positives	14%		14%		13%	
False positives	9%		8%		11%	
False negatives	1%		1%		2%	
Total	100%		100%		100%	
Accuracy	90%		93%		87%	
Patients to biopsy	**51**		**59**		**58**	

Table C15c Summary patient pathway Incidence 30%

Patient numbers 1000	Incidence 30%		Incidence 30%		Incidence 30%	
	Median		Best Case		Worst Case	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
F2-F4	78.75	82.20	90.20	80.00	75.00	76.15
True negatives	58%		56%		53%	
True positives	24%		27%		23%	
False positives	12%		14%		17%	
False negatives	6%		3%		8%	
Total	100%		100%		100%	
Accuracy	81%		85%		76%	
Positives	**361**		**411**		**392**	

	Incidence 65%		Incidence 66%		Incidence 57%	
	Median		Best Case		Worst Case	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
F3-F4	85.30	86.00	91.57	87.37	80.89	85.50
True negatives	60%		61%		60%	
True positives	26%		27%		24%	
False positives	10%		9%		10%	
False negatives	4%		3%		6%	
Total	100%		100%		100%	
Accuracy	85%		91%		84%	
Positives	**128**		**149**		**135**	

	Incidence 65%		Incidence 76%		Incidence 71%	
	Median		Best Case		Worst Case	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
F4	90.50	89.35	93.85	91.08	87.50	86.53
True negatives	63%		64%		61%	
True positives	27%		28%		26%	
False positives	7%		6%		9%	
False negatives	3%		2%		4%	
Total	100%		100%		100%	
Accuracy	91%		93%		87%	
Patients to biopsy	**84**		**98**		**87**	

9.5.7 Present results of deterministic multi-way scenario sensitivity analysis described in table C10.2.

Not undertaken

9.5.8 Present results of the probabilistic sensitivity analysis described in table C10.3.

Not undertaken

9.5.9 What were the main findings of each of the sensitivity analyses?

There were very limited changes in the outcome between our best case worst case and median case scenarios at any of the incidence levels.

Where VTq replaces biopsy in all cases savings are very large. Where only a proportion of patients would undergo biopsy then the cost of VTq shows lower savings.

Table C16a Sensitivity analysis findings all patients receive biopsy

		Best Case			Worst Case		
Incidence		**patients**	**Cost**	**Total**	**patients**	**Cost**	**Total**
10%	Cost of Vq	1000	£ 15	£ 15,020	1000	£ 15	£ 15,020
	Total cost to biopsy	1000	£ 615	£ 615,000	1000	£ 615	£ 615,000
	Biopsy cost - VTq	46	£ 615	£ 28,169	48	£ 615	£ 29,794
	Treat false postives	4	£ 10,000	£ 44,551	7	£ 10,000	£ 74,256
	Saving			**£ 527,261**			**£ 495,930**
15%	Cost of Vq	1000	£ 15	£ 15,020	1000	£ 15	£ 15,020
	Total cost to biopsy	1000	£ 615	£ 615,000	1000	£ 615	£ 615,000
	Biopsy cost - VTq	59	£ 615	£ 35,996	58	£ 615	£ 35,762
	Treat false postives	6	£ 10,000	£ 56,682	9	£ 10,000	£ 88,308
	Saving			**£ 507,301**			**£ 475,911**
30%	Cost of Vq	1000	£ 15	£ 15,020	1000	£ 15	£ 15,020
	Total cost to biopsy	1000	£ 615	£ 615,000	1000	£ 615	£ 615,000
	Biopsy cost - VTq	98	£ 615	£ 60,152	87	£ 615	£ 53,359
	Treat false postives	9	£ 10,000	£ 93,152	13	£ 10,000	£ 127,242
	Saving			**£ 446,677**			**£ 419,379**

If in the cohort of 1000 patients only 200 would have undergone biopsy then the cost savings are far less and are heavily dependent on the treatment that those assessed as false positives undertake.

This chart does not show the benefit gained by the 1000 patients who received fibrosis assessment using VTq. A proportion of these patients will have had undiagnosed severe fibrosis identified and will go on to treatment with resultant cost but also savings as they will not advance to cirrhosis.

Table C16b Sensitivity analysis findings 20% of patients receive biopsy

		Best Case			Worst Case		
Incidence		**patients**	**Cost**	**Total**	**patients**	**Cost**	**Total**
10%	Cost of Vq	1000	£ 15	£ 15,020	1000	£ 15	£ 15,020
	Total cost to biopsy	200	£ 615	£ 123,000	200	£ 615	£ 123,000
	Biopsy cost - VTq	46	£ 615	£ 28,169	48	£ 615	£ 29,794
	Treat false postives	4	£ 10,000	£ 44,551	5	£ 10,000	£ 49,182
	Saving			**£ 35,261**			**£ 29,003**
15%	Cost of Vq	1000	£ 15	£ 15,020	1000	£ 15	£ 15,020
	Total cost to biopsy	200	£ 615	£ 123,000	200	£ 615	£ 123,000
	Biopsy cost - VTq	59	£ 615	£ 35,996	58	£ 615	£ 35,762
	Treat false postives	6	£ 10,000	£ 56,682	9	£ 10,000	£ 88,308
	Saving			**£ 15,301**			**-£ 16,089**
30%	Cost of Vq	1000	£ 15	£ 15,020	1000	£ 15	£ 15,020
	Total cost to biopsy	200	£ 615	£ 123,000	200	£ 615	£ 123,000
	Biopsy cost - VTq	98	£ 615	£ 60,152	87	£ 615	£ 53,359
	Treat false postives	9	£ 10,000	£ 93,152	8	£ 10,000	£ 84,277
	Saving			**-£ 45,323**			**-£ 29,656**

It is most likely that the number of patients receiving VTq and then biopsied will be lower than the number indicated. Not least because the decision will be taken based on additional evidence. Likewise not all patients will receive a lengthy course of treatment. The table below shows the outcome if only two thirds of patients' receive biopsy and the treatment cost per patient is £6500

Table C16c Sensitivity analysis findings 20% of patients receive biopsy

		Best Case			Worst Case		
Incidence		**patients**	**Cost**	**Total**	**patients**	**Cost**	**Total**
10%	Cost of Vq	1000	£ 15	£ 15,020	1000	£ 15	£ 15,020
	Total cost to biopsy	200	£ 615	£ 123,000	200	£ 615	£ 123,000
	Biopsy cost - VTq	30	£ 615	£ 18,591	32	£ 615	£ 19,664
	Treat false postives	4	£ 6,500	£ 28,958	5	£ 6,500	£ 31,968
	Saving			**£ 60,431**			**£ 56,347**
15%	Cost of Vq	1000	£ 15	£ 15,020	1000	£ 15	£ 15,020
	Total cost to biopsy	200	£ 615	£ 123,000	200	£ 615	£ 123,000
	Biopsy cost - VTq	39	£ 615	£ 23,758	38	£ 615	£ 23,603
	Treat false postives	6	£ 6,500	£ 36,843	9	£ 6,500	£ 57,400
	Saving			**£ 47,379**			**£ 26,977**
30%	Cost of Vq	1000	£ 15	£ 15,020	1000	£ 15	£ 15,020
	Total cost to biopsy	200	£ 615	£ 123,000	200	£ 615	£ 123,000
	Biopsy cost - VTq	65	£ 615	£ 39,700	57	£ 615	£ 35,217
	Treat false postives	9	£ 6,500	£ 60,549	8	£ 6,500	£ 54,780
	Saving			**£ 7,731**			**£ 17,983**

9.5.10 What are the key drivers of the cost results?

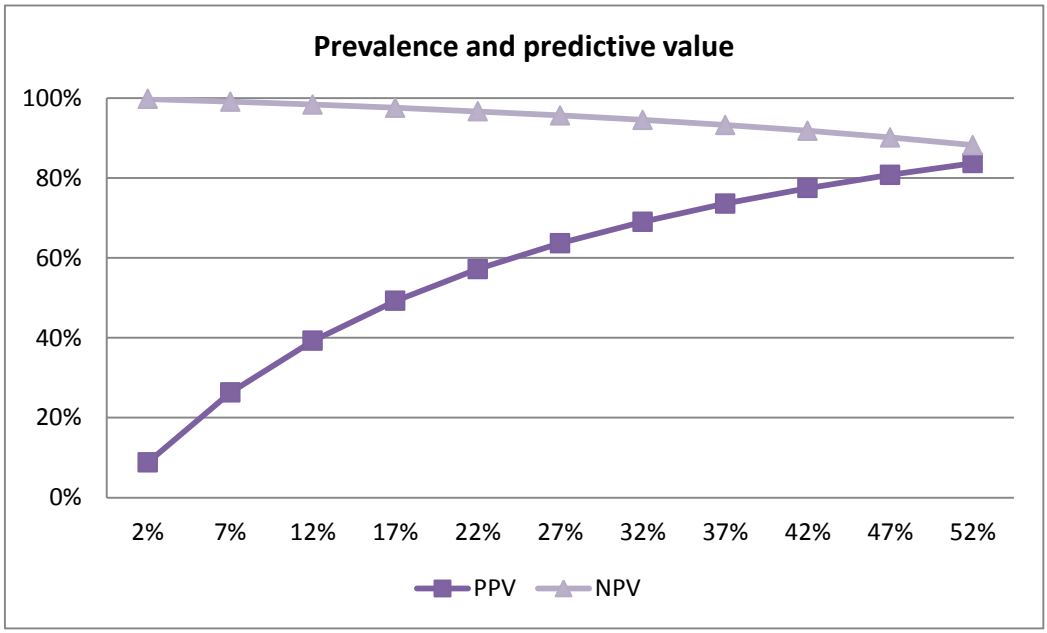
The cost of VTq measurement is low for any level of throughput whether one takes the bottom up approach or the PbR tariff. The cost of TE measurement may be of equivalent cost to that of VTq in high throughput sites but at moderate throughputs is more expensive.

The cost of liver biopsy is relatively expensive. The true cost is unclear as this will depend on the type of procedure performed. If the patient mix contains more cases of cirrhosis and these receive biopsy this may be through the more expensive transjugular route.

The accuracy of the methodology depends heavily on the cut off values assigned which in turn are a function of the clinical question asked. The incidence of disease and therefore the patients the clinic sees is the major influence.

Prevalence/incidence is an important factor. The chart below shows how the Positive and Negative predictive values change depending on prevalence where Sensitivity =90% and Specificity 80%. Best Case >= F2

Figure C1 Prevalence and Predictive Value, Sen=90%,Se=80%



Miscellaneous results

9.5.11 Describe any additional results that have not been specifically requested in this template. If none, please state.

Sensitivity and specificity measurements were reviewed from a number of papers . The quality was assessed based on the patient population hepatitis/non hepatitis and the depth from where the VTq measurement was made. The bottom four group of papers was not included due to time constraints but we believe that will not have altered the outcome.

Table C17a Papers reviewed for Accuracy data

Shah et al 2013	HepB/C	2.0cm	A
Crespo et al 2012	HCV POST-TX	2.5cm	A
Takahashi et al 2010	HepB/C	2-3cm	A
Yamada et al 2014	Hep C	2cm	A
Ye et al 2012	Hep B	2cm	A
Ref 47	Hep C	1cm	B
Ref 48	Unclear	1-2cm	B
Ref 61	Hep C	2.5-4.5 below skin	B
Ref 44	Mixed	META	B
Ref 18	Hep	META	B
Ref 52	Hep C	3.0-5.5 below skin	B
F. Rust et al 2009	HCV, HBV	Unclear	B
Toshima et al 2011	HCV,HBV, ALCOHOL	Unclear	B
AVERAGE			
A			
B			
25th percentile			
Median			
75th percentile			
Silva et al 2014	Hep B	2cm	A
Liu et al 2014	Hep B	Unclear	B
Yap et al 2013	Hep C	5cm below skin	B
Chen et al 2013	Hep C	Unclear	B

Table C17b F>=2 Published Se,Sp,PPV,NPV,Accuracy, Cut off

F>=2	Se	Sp	PPV	NPV	Accuracy	Cut off
Shah et al 2013	78.5	84.4	81.6	81.7		
Crespo et al 2012	89.0	80.0				1.39
Takahashi et al 2010	91.4	80.0	86.6	85.0	87.3	1.34
Yamada et al 2014	92.5	76.2	64.9	95.5		1.26
Ye et al 2012						
Ref 47	77.5	86.7	94.8	54.9	79.6	1.20
Ref 48	88.7	67.5	64.5	90.0	76.5	1.27
Ref 61	67.8	92.9	93.0	67.2		1.31
Ref 44	79.0	85.0	91.0	66.0		1.34
Ref 18	75.0	87.0				1.30
Ref 52	81.0	70.0	10.0	0.9		1.31
F. Rust et al 2009	72.9	93.8	97.2	53.6		1.35
Toshima et al 2011	75.0	76.0	76.0	75.0		1.52
AVERAGE	80.7	81.6				1.3
A	90.2	80.0	Best Case			
B	77.1	82.4				
25th percentile	88.8	86.8				
Median	78.8	82.2	Median Case			
75th percentile	75.0	76.2	Worst Case			
Silva et al 2014	89.3	87.0	89.2	87.0		1.31
Liu et al 2014	84.0	83.1	79.1	89.4	83.5	1.27
Yap et al 2013	68.0	66.0	74.0	59.0		1.34
Chen et al 2013	74.1	87.0	90.9	65.6		1.55

Table C17c F>=3 Published Se,Sp,PPV,NPV,Accuracy, Cut off

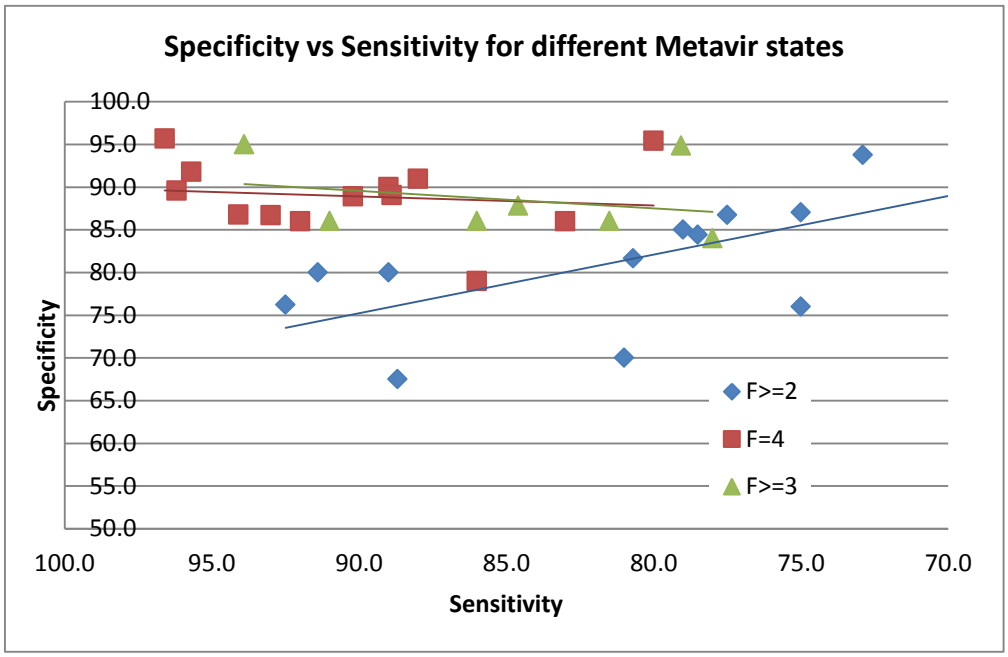
F>=3	Se	Sp	PPV	NPV	Accuracy	Cut off
Shah et al 2013			n/a	n/a	n/a	
Crespo et al 2012			n/a	n/a	n/a	
Takahashi et al 2010	96.2	79.3	80.6	95.8	87.3	1.44
Yamada et al 2014	84.6	87.8	64.7	95.6		1.46
Ye et al 2012	93.9	95.0				1.69
Ref 47			n/a	n/a	n/a	
Ref 48			n/a	n/a	n/a	
Ref 61	79.1	94.8	91.9	85.9		1.64
Ref 44	86.0	86.0	82.0	89.0		1.55
Ref 18						
Ref 52	91.0	86.0				
F. Rust et al 2009	81.5	86.0	88.0	87.2		1.55
Toshima et al 2011	78.0	84.0	72.0	88.0		1.69
AVERAGE	86.3	87.4				1.57
A	91.6	87.4	Best Case			
B	83.1	87.4				
25th percentile	91.7	89.6				
Median	85.3	86.0	Median Case			
75th percentile	80.9	85.5	Worst Case			
Silva et al 2014	94.4	90.9	85.0	96.8		1.68
Liu et al 2014						
Yap et al 2013	95.0	86.0	74.0	98.0		1.55
Chen et al 2013	90.2	89.5	80.4	95.0		1.81

Table C17d F=4 Published Se,Sp,PPV,NPV,Accuracy, Cut off

F=4	Se	Sp	PPV	NPV	Accuracy	Cut off
Shah et al 2013	96.6	95.7	82.3	99.3	91.4	1.80
Crespo et al 2012	89.0	90.0				
Takahashi et al 2010	94.1	86.8			88.0	1.70
Yamada et al 2014						2.00
Ye et al 2012	95.7	91.8				1.80
Ref 47	96.2	89.6	78.1	98.3		1.80
Ref 48	93.0	86.7	73.6	96.9		2.11
Ref 61	80.0	95.5	90.3	90.0		1.92
Ref 44	92.0	86.0	71.0	97.0		1.75
Ref 18	88.0	91.0				1.79
Ref 52	83.0	86.0			91.0	1.80
F. Rust et al 2009	88.9	89.1	76.2	95.3		
Toshima et al 2011	86.0	79.0	51.0	95.0		1.88
AVERAGE	90.2	88.9				1.85
A	93.9	91.1	Best Case			
B	88.4	87.9				
25th percentile	93.3	90.3				
Median	90.5	89.4	Median Case			
75th percentile	87.5	86.5	Worst Case			
Silva et al 2014	100.0	95.2	81.8	100.0		1.95
Liu et al 2014	93.1	76.8	92.4	83.9	88.8	1.65
Yap et al 2013						1.80
Chen et al 2013	88.9	79.8	42.1	97.8	81.1	1.98

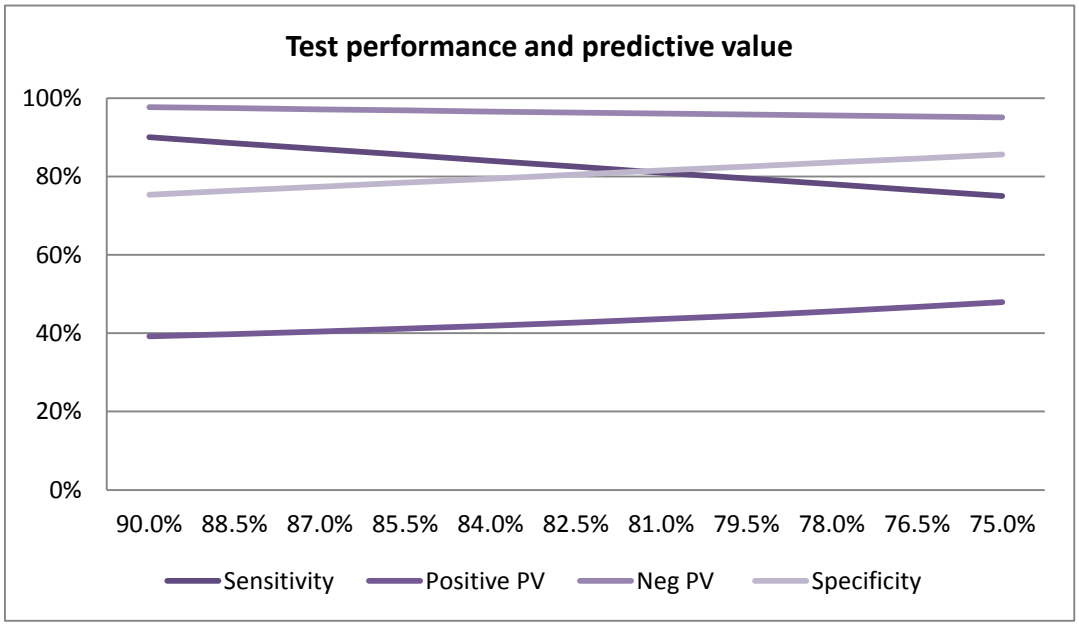
*Below we show the sensitivity analysis which shows the relationship of sensitivity to specificity for the lowest cut off (F>=2) where specificity = sensitivity * -0.685+1.37 and the resultant positive and negative predictive values.*

Figure C2 Specificity vs Sensitivity for Metavir status



The negative and positive predictive values shows limited change over the range for sensitivity and specificity. The incidence is 15%. The result shows that the test is good for selecting those patients who probably do not have fibrosis >=F2.

Figure C3 Test performance and predictive value



9.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

9.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1 and sections 3.2 and 7.4.4.

No sub groups were included

9.6.2 Define the characteristics of patients in the subgroup(s).

No sub groups were included

9.6.3 Describe how the subgroups were included in the cost analysis.

No sub groups were included

9.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis).

No sub groups were included

9.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

No sub groups were included

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The studies described in Section 8 have addressed the question of the cost of providing an elastography service (Fibroscan). VTq can be substituted in these studies (based on a similar accuracy to Fibroscan for the population) and that for high patient throughputs the costs of the two techniques are very similar and both show savings versus liver biopsy. We comment elsewhere why we believe that a lower patient throughputs or if there is a high number of patients exhibiting symptoms for which Fibroscan is contra indicated VTq is the more cost effective option.

There are a number of different approaches taken to show the cost benefits of elastography versus liver biopsy.

- *Comparing the number of correct diagnosis of elastograpy vs liver biopsy (Steadmann et al, CEP 08053) for a hypothetical cohort.*
- *An audit of costs using 'real world data' to assess the introduction of elastography into a care pathway (Whitty and Tallis). This study is of interest as it shows the savings that a regime using elastography can deliver. It is not applicable to compare this approach with the results we show.*
- *Comparing cirrhosis surveillance strategies (Cannavan et al).*
- *Cost-effectiveness, and effect on patient outcomes (Stevenson et al). This study focussed on alcoholic liver disease and therefore its inclusion was primarily as this group had presented and analysed a number of factors associated with the use of LB and TE.*

Method A Comparing the number of correct diagnoses assumes that all patients either have elastography or liver biopsy. This is unrealistic as not all patients diagnosed with HBV or C will receive biopsy. The current model is to biopsy patients with repeatedly abnormal LFT results and a normal diagnostic ultrasound. We have no indication of the results of this approach.

This is also the major weakness of the studies reviewed in section 8. The choice of prevalence of moderate fibrosis/severe fibrosis /cirrhotic disease is unclear. Cannavan et al reference papers which report that in the UK ~10% of HCV patients annually will receive a biopsy. (50% every 5 years/87% in 7.6 years). If we assume that some patients will receive more than one biopsy over this period then in a cohort of 1,000 patients in excess of 150 patients may expect to receive a biopsy.

Method B is to analyse the cost of providing a screening strategy on an annual basis and looking at how many patients would have been diagnosed using the existing model and how many will be diagnosed if we incorporate elastography. We have not included this analysis but would expect the cost of Vtq to be equivalent or less costly to the results presented by Canavan et al.

None of the papers has commented on the outcome for false positive patients which we presume will receive unnecessary treatment and at a cost.

9.8 Interpretation of economic evidence

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

A number of studies have been published which look at the cost of TE (Fibroscan) and liver biopsy. These studies show liver biopsy to be an expensive technique. Like others we have not costed liver biopsy de novo but have used published costs (NHS PbR)). The cost of TE depends on the number of patients diagnosed and the staff roster. The published evaluations have taken high throughput scenarios and have often failed to assess staffing

costs which have been assumed as 'free good' notwithstanding that an increased headcount was part of the proposal for the unit.

9.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

Yes – the cost analysis is appropriate to either primary or secondary/tertiary care settings. In each of these settings we have envisaged the measurements will be made by a radiographer but there is no reason why they cannot be made by a suitably qualified clinician. Both VTq and Fibroscan require the operator to undertake a minimum level of activity to maintain competence. The analysis is relevant to both HBV and HCV patients but is also of interest to those monitoring fibrosis from other etiologies.

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The main strength of the analysis is that the cost of elastography is minimal compared with that of liver biopsy and therefore in comparing the two there is little point in agonising over the precise cost of the elastography examination.

VTq vs TE

Staff costs are a significant cost of the elastography measurements. VTq is easier to cost as fewer assumptions need to be made of how staff are deployed. In institutions with a low case load (1000 studies per year) the total cost of operating Fibroscan over VTq may be as high as £35,180.

The relative sensitivities and specificities of each method. If Fibroscan has a lower accuracy relative to VTq then this may lead to more patients being sent for biopsy. The range of values published for each method point to them being broadly similar. The difference between the best and worst case VTq scenarios has been shown to deliver savings of ~£5,000 to ~£10,000.

Differences in accuracies between methods would be expected to save/cost similar sums.

The failure rate of each method. For 1,000 patients for each percentage point the rejection rate of Fibroscan is higher than VTq the additional cost will be £5,690, the cost of a biopsy. If the rates are 4% VTq vs 7% TE then this equates to £22,760

The major weakness is a thorough understanding of the number of patients who would have been biopsied prior to an elastography service for HBV, HCV and how this changed subsequent to the arrival of this service.

9.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Detailed figures for the prevalence of disease at clinics which HBV and HCV patients attend. The number of patients undergoing liver biopsy in England was recorded as 12,595 (OPCS J13.2). Source: Hospital Episode Statistics, Admitted Patient Care - England, 2011-12 http://www.hscic.gov.uk/catalogue/PUB08288

Our assumption indicates that all patients at the outset will receive liver biopsy but in fact this is unlikely to be the case. The confusion arises as many centres operate Fibroscan or undertake laboratory test such as Fibrotest which triages patients away from biopsy. If we assume at a prevalence level for >=F2 of 10% patients assessed by elastography and seen to be below the threshold would have also been selected by single or combinations of other tests then ~200 patients may have been expected to receive a liver biopsy. Savings will then be ~£35,000.

We have not assessed the utility of the methods in following therapy.

We have not assessed the delay in patients receiving a liver biopsy and whether this has any cost implications. The Australian paper (Whitty et al) looked at this scenario but in Australia.

It is known that liver biopsy pre-assessment appointments and the diagnostic test itself has an above average DNA (do not attend) rate reflecting the risks associated with the procedure and the client group

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10 Appendices

10.1 Appendix 1: Search strategy for clinical evidence (section 7.1.1)

The following information should be provided:

10.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

Medline

Embase

Medline (R) In-Process

The Cochrane Library.

The following databases were searched for relevant studies from 2000 to May 2014:

MEDLINE (2000– May 2014 Week 3) (PubMed Central)

EMBASE (2000–2014 Week 20) (OvidSP)

Cochrane Database of Systematic Reviews (CDSR) (The Cochrane Library Issue 5 of 12, May 2014) (Wiley) 1 Found (ARFI) 1 Found (Elastography)

Database of Abstracts of Reviews of Effects (DARE) (1 January 2011–20 May 2014) (CRD website http://www.crd.york.ac.uk/CRDWeb/ResultsPage.asp) 3 found

Health Technology Assessment (HTA) database (1 January 2011–20 May 2014) (CRD website http://www.crd.york.ac.uk/CRDWeb/ResultsPage.asp) 1 found Health Technology Assessment 2012; Vol. 16: No. 4

No specific searches were undertaken to identify grey literature and completed and ongoing trials.

Searches were undertaken to identify studies using Virtual Touch Quantification (VTq) software and Transient elastography for the diagnosis of fibrosis associated with hepatitis.

Search strategies were developed for each database and the keywords adapted accordingly. We used the term ARFI, the generic description of the technique, in preference to Virtual Touch Quantification (VTq) or VTq as this was not always present in the title or abstracts. Restrictions on language or publication status were applied. Animal studies were not included.

Electronic searches were undertaken on conference abstracts.

The search term used was ARFI. The search term ARFI identified sessions in which talks concerning ARFI were presented. We selected abstracts for review where liver or hepatic and fibrosis were identified. The meeting organisers have an interest in associating like papers in the same session.

We only searched the 2013 year assuming that earlier abstracts will have been submitted as full papers and be identified in the previous searches.

EFSUMB (EUROSON)

2014: www.thieme-connect.com was not interogated

Radiological Society of North America (RSNA)

In 2013 all abstracts were situated in the session: Gastrointestinal (Hepatic Fibrosis Imaging)

2013: http://rsna2013.rsna.org/search/search.cfm 4 abstracts

2012: http:// rsna2012.rsna.org/search/search.cfm 3 Abstracts

2011: http:// rsna2011.rsna.org/search/search.cfm 5 abstracts

European Congress of Radiology (ESR) In 2013 all abstracts were situated in the session: SS 101b Liver fibrosis and cirrhosis: elastography and biomarkers

2013: http://www.myesr.org/cms/website.php?id=/en/ecr_2013/book_of_abstracts.htm 0 abstracts

Studies collected by Siemens were checked against the project reference database and any studies not already identified by our searches were screened for inclusion following the process described above. The studies eliminated at this stage were those which did not refer to liver or hepatitis in the title or abstract.

10.1.2 The date on which the search was conducted.

Week 22 2014

10.1.3 The date span of the search.

2009 to date

MEDLINE (PubMed 2000– May 2014 Week 3) and EMBASE (searched 20/05/2014)

1. Elastography [Title/Abstract]	PubMed 2729	Embase 4261
2. elasticity imaging [Title/Abstract]	PubMed 228	Embase 249
3. Virtual Touch Quantification [Title/Abstract]	PubMed 0	Embase 12
4. Virtual Touch Quantification	PubMed 58	
5. VTq	PubMed 60	Embase 50
6. ARFI[Title/Abstract]	PubMed 288	Embase 532
8. ARFI	PubMed 429	
9. hir te [Title/Abstract]	PubMed 0	Embase 0
10. hirte [Title/Abstract]	PubMed 1	Embase 4
11. hepatitis[Title/Abstract]	PubMed 14,471	Embase 207828
12. liver stiffness[Title/Abstract]	PubMed 747	Embase 1771
13. liver fibrosis[Title/Abstract]	PubMed 7504	Embase 11794
14. hepatic fibrosis[Title/Abstract]	PubMed 5330	Embase 7553
15. fibroscan [Title/Abstract]	PubMed 414	Embase 1290
16. Acoustic Radiation Force		Embase 0

PUBMED

(ARFI) AND hepatitis PubMed 41

Search ((((VTq) AND hepatitis) AND Elastography)) AND liver PubMed 37

Search ((((VTq) AND hepatitis) AND Elastography)) AND liver [Title/Abstract] PubMed 27

EMBASE

1.ARFI[Title/Abstract] or VTq[Title/Abstract] or Virtual Touch Quantification[Title/Abstract] 563

2.Hepatitis[Title/Abstract] or Liver Stiffness[Title/Abstract] or Liver Fibrosis[Title/Abstract] or Hepatic Fibrosis[Title/Abstract] 219,848

3. 1 and 2 =293

4. 1 and hepatitis [Title/Abstract] 131

5. 1 and hepatitis 155

6. Transient Elastography [Title/Abstract] or Fibroscan [Title/Abstract] 224

7. 1 and 5 and hepatitis 71

8. 1 and 5 and hepatitis and fibrosis [Title/Abstract] 70

10.1.4 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

None

10.1.5 The inclusion and exclusion criteria.

Inclusion

Papers in which ARFI was used and where liver biopsy (LB) was the reference. Papers in which Transient Elastography was used on the same patient group as ARFI. The patient population had either Hepatitis B or Hepatitis C or where patients with these etiologies comprised the majority.

Exclusion

There are a limited number of groups/authors who have published studies and there are a number of what appear to be duplicated papers with the same patients or where there is considerable overlap. These were excluded. Papers

presented at meetings were excluded where the inclusion points were unclear or where these submissions overlapped full publications.

10.1.6 The data abstraction strategy.

Data were extracted by one reviewer to the data extraction forms. Where multiple publications of the same study were identified the most recent study was selected.

10.2 Appendix 2: Search strategy for adverse events (section 7.7.1)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Response

10.2.2 The date on which the search was conducted.

Response

10.2.3 The date span of the search.

Response

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

10.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

10.2.6 The inclusion and exclusion criteria.

Response

10.2.7 The data abstraction strategy.

Response

10.3 Appendix 3: Search strategy for economic evidence (section 8.1.1)

The following information should be provided.

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

The following were reviewed for the clinical evidence but also acted as searches for economic evidence.

Cochrane Database of Systematic Reviews (CDSR) (The Cochrane Library Issue 5 of 12, May 2014) (Wiley) 1 Found (ARFI) 1 Found (Elastography)

Database of Abstracts of Reviews of Effects (DARE) (1 January 2011–20 May 2014) (CRD website http://www.crd.york.ac.uk/CRDWeb/ResultsPage.asp) 3 found

Health Technology Assessment (HTA) database (1 January 2011–20 May 2014) (CRD website http://www.crd.york.ac.uk/CRDWeb/ResultsPage.asp) 1 found Health Technology Assessment 2012; Vol. 16: No. 4

10.3.2 The date on which the search was conducted.

Week 26 2014 (28/06/2014)

10.3.3 The date span of the search.

MEDLINE (2009– June 2014) (PubMed Central)

EMBASE (2009–2014) (OvidSP)10.3.2

10.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

1. ARFI [Title/Abstract]	*PubMed 288*
2. Economic	*PubMed 0*
1. Elastography [Title/Abstract]	

2. Economic *PubMed 22*

EMBASE

#17 'cost'/exp OR cost OR economic:ab,ti	*673,132*
#18 elastography:ab,ti4,	*273*
#17 AND #	*18 105*
#20 liver:ab,ti	*749,811*
#21 'liver'/exp OR liver OR hepatic:ab,ti	*1,247,127*
(#17 AND #18) AND #21	*61*

We reviewed the titles of these 61 items and selected ten where we reviewed the abstracts. Of these six were viewed as potentially relevant. One of these was a duplicate and therefore we were left with four to take to the full paper stage.

10.1.4 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

10.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

In addition we included a paper from CEP (CEP08053) Cost effectiveness of ultrasound elastography in the assessment of liver fibrosis (2009)

Search for information covering accuracy (sensitivity and specificity)

("01/01/2012"[PDAT] : "3000"[PDAT]) AND ((arfi[Title/Abstract] AND ("sensitivity and specificity"[MeSH Terms] OR ("sensitivity"[All Fields] AND "specificity"[All Fields]) OR "sensitivity and specificity"[All Fields] OR "sensitivity"[All Fields])) AND hepatitis[Title/Abstract]) AND hasabstract[text] found 14 papers of which 3 were additional to those found in the clinical search.

In addition we uncovered 3 recent papers and 1 abstract outside this information search

10.4 Appendix 4: Resource identification, measurement and valuation (section 9.3.2)

The following information should be provided.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

Outside the resources identified in the papers reviewed in Section 8 the other resource information was from various NHS sources which can only be found by 'trawling' various NHS and government websites.

10.4.2 The date on which the search was conducted.

June 2014

10.4.3 The date span of the search.

June 2014

10.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

N/a

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

https://www.gov.uk/government/publications/payment-by-results-pbr-operational-guidance-and-tariffs 07_-_Tariff_information_spreadsheet_2013-14_v6.xls

10.4.6 The inclusion and exclusion criteria.

N/a

10.4.7 The data abstraction strategy.

Tedious

HBV

10.5 Appendix 5: Questions to clinical advisors (section 9.2.5)

HTA Appraisal

The document is our answer to the question. It will then be reviewed and added to by the appraisal group contracted by NICE prior to a final recommendation later this year. Liver biopsy is expensive and painful, elastography is cheap but is it good or is it cheerful?

The analysis is on the basis of published materials and a de novo cost analysis. There are weaknesses in the published material. The major weakness is the adequacy of biopsy as a comparator. A secondary weakness for VTq is how the exams are acquired and the cut of values used. Best practice in a laboratory environment would be to establish a local 'normal range' but this may not occur.

On pages 9.2.5 and 9.3.4 we are asked to ask clinical advisors to review the evidence submitted.

Part A

The flow charts Fig A2/3/4/5 show the current and future diagnostic algorithms. The future algorithm should show that VTq could be performed as an add on to the diagnostic ultrasound as a one stop shop. It shouldn't show that this is taking place in general practice rather that the referral is from general practice.

Q. Between the extremes is the patient route reasonable?

Part B

The summary of this section is that the accuracy of VTq is similar to that of Fibroscan. Cut off values for patients with Hep B and Hep C differ but in later analyses we have not taken this into account due to limited results for Hep B patients.

The AUROC values for both techniques are shown on table X for the selected papers. The median values are highlighted. The accuracy of VTq is summarised in terms of sensitivity and specificity for >=F2,F3/F4 and F4 in Part C. The accuracy of the technique improves with severity of fibrosis.

Part C

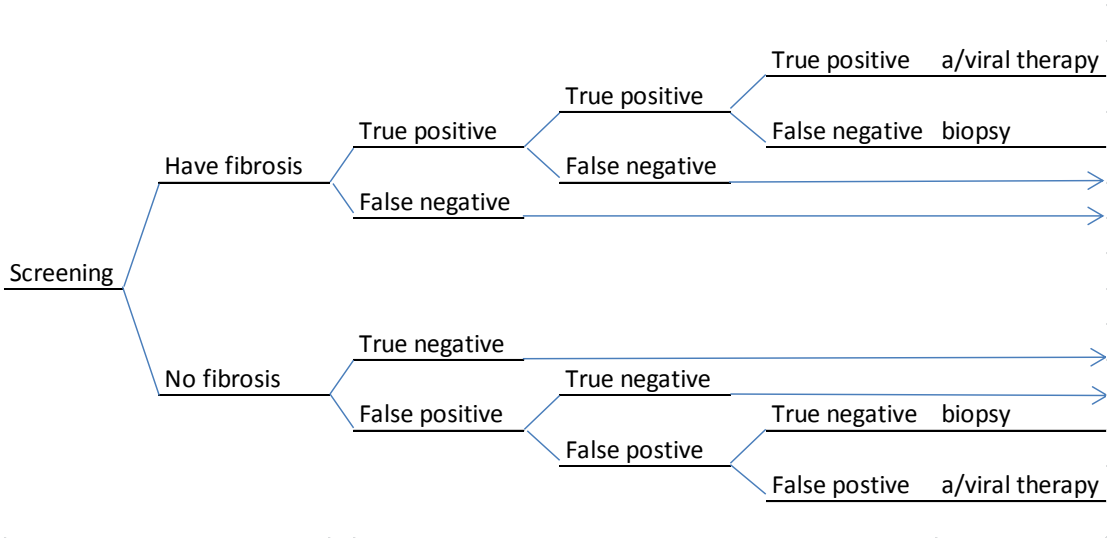
Section 8 Existing economic appraisals

There are no economic appraisals of ARFI. There are a number of appraisals of Fibroscan. The selected papers are listed Section 8.2. I have yet to appraise these but this is a box ticking exercise.

Have we been too selective is there anything obviously missing?

Section 9 De Novo analyisis

Figure 9.14 This algorithm summarises the analysis.



It assumes that:

- patients below the lower cut off value 'are sent home'. Patients above the cut off are re evaluated.
- If their cut off value is below the cut off for F3/F4 they are regarded as 'negative' and again 'sent home'.
- Patients with values above the cut off are re evaluated and if they are above the threshold for F4 are assumed to have cirrhosis.
- Those in this group who are below the F4 threshold (negatives) are offered biopsy as their status is unknown.
- Those diagnosed with F3/F4 fibrosis by VTq will not be biopsied requiring a small number to receive anti viral therapy.

Table C14 page 117 summarises the outcome of this algorithm for different rates of incidence based on the best case, median case and worst case scenarios.

Is this reasonable or are the selection criteria different?

Cost

NHS costs. The cost of biopsy is taken as the NHS published cost. The cost of ultrasound plus VTq could either be two separate exams or VTq could be regarded as an add on to the diagnostic ultrasound. Fibroscan is an ultrasound study.

Real costs – Fibroscan cost of the equipment plus service and written off over seven years. The cost of VTq is the cost of using the ultrasound on a sessional basis with either 5 or ten patients scanned during the session and written off over five years. Staffing for VTq is sessional. Staffing for Fibroscan is 0.5 WTE lower throughputs/1.0 WTE higher throughputs. Table C11 summarises the results. Table C12 shows the savings for 1000 patients. The main message is that VTq is very cheap especially if the ultrasound is used elsewhere. Fibroscan can meet these costs but only with high referral numbers. There is an additional cost associated with Fibroscan and that is the number of patients who cannot be scanned. We have assumed this to be 7% for Fibroscan on 3% for VTq. Published evidence is vague. The newer probe introduced by Fibroscan will have improved the rejection rate. Every one of these patients receiving a biopsy will add ~£600 to the Fibroscan account.

Are we being fair in how we have viewed cost?

We have a few pieces of info missing

What are the number of patients who would be expected to have elastography pa in your hospital? (This will be the total number not only those referred for Hep B and C)

While we assume that the cohort of patients is a new set each year in reality this will be the patients screened in past years and new patients with others leaving the cohort due to death…

Does this lead to the prevalence level rising year on year or is it stable?

We have assumed that in a group of 1000 patients diagnosed with chronic HepB or C that all would have had liver biopsy prior to the advent of elastography. I suspect this isn't the case.

Of the 1,000 patients how many would receive biopsy on the basis of clinical evidence, lab tests, radiology?

If these patients are taken out of the mix how will this affect the incidence of F2/F3/F4?

Appendix 6: Cost

Capital	VTq	Fibroscan		
Machine	£ 59,700	£ 79,950		Type
Maintenance	£ 2,687	£ 4,797	£ (,000)	8% of assett
VTq	£ 4,415	£ -	£ (,000)	4% of assett
TOTAL	**£ 19,042**	**£ 16,218**	**£ (,000)**	**Annual Cost**

Consumables	VTq	Fibroscan		
Storage	0	0		images per case
Consumables	0	0	£	u/s gell
Consumables	0	0	£	patient recovery
TOTAL	0	0	£	per case

Staffing	VTq	Fibroscan			
Clinician	0	0		Consultant	#
Technical	£ 54,275	£ 45,366		Senior 1 / Super 3	#
Scientific	0	0			
Administrative	0	0			
TOTAL	**£ 54,275**	**£ 45,366**	**£ (,000)**		

Factors	VTq	Fibroscan				
Insurance	597.0	550.0	£ (,000)	% of assett		1%
Rent	1000.0	1000.0	£ (,000)	per sq m	£	250
Utilities	120.0	120.0	£ (,000)	per sq m	£	30
Cleaning & Maintenance	80.0	80.0	£ (,000)	per sq m	£	20
Legal & Accounting	0.0	0.0	£ (,000)	% of project		1%
Marketing	0.0	0.0	£ (,000)	% of project		1%
Management Overhead	0.0	0.0	£ (,000)	% of project		5%
Portering	0.0	0.0	£ (,000)	% of project		5%
TOTAL	**£ 1,797**	**£ 1,750**	**£ (,000)**			

11 Related procedures for evidence submission

11.1 Cost models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the External Assessment Centre, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the External Assessment Centre with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

11.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the medical technology consultation document and medical technology guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted

correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the External Assessment Centre and the Medical Technologies Advisory Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

11.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Medical Technologies Advisory Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).