Virtual Touch Quantification to diagnose and monitor liver fibrosis

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Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

KiTEC references have been provided using the NICE style, followed by sponsor references in square brackets in the clinical and technical sections for ease of comparison where available.

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Abbreviations

ARFI	Acoustic Radiation Force Impulse
AUROC	Area under receiver operating characteristic
CI	Confidence Interval
DARE	Database of Abstracts of Reviews of Effects
DTA	Diagnostic test accuracy
EAC	External Assessment Centre
HTA	Health Technology Assessment
ITT	Intention to treat
LB	Liver Biopsy
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPV	Negative Predictive Value
PbR	Payment by results
PPV	Positive Predictive Value
PWID	People who inject drugs
RCT	Randomised Controlled Trials
TE	Transient Elastography
VTq	Virtual Touch Quantification

1. Summary

1.1 Scope of the sponsor's submission

The sponsor submitted clinical and economic evidence related to Virtual Touch Quantification (VTq) and the two comparators listed in the scope, liver biopsy and Transient Elastography (TE). The sponsor submitted some of the available evidence relating to VTq and its comparators, and the EAC identified several additional papers within their systematic review, which were either not identified or excluded by the sponsor.

The cost analysis has assessed the impact of the technology (VTq) and comparators (TE and liver biopsy) in the patient population as specified by the scope. This matches with the cost analysis specified in the final scope, although the EAC identified issues related to the model structure and specific assumptions used in the model.

1.2 Summary of clinical evidence submitted by the sponsor

The EAC reviewed all of the sponsor submitted evidence, including sponsor-excluded studies. Clinical evidence was provided on the intended intervention and both scope-specified comparators. The sponsor provided clinical evidence based on 23 studies (a combination of conference abstracts and full publications). On further evaluation, the sponsor refined this evidence to 11 studies for full review, as the other 12 studies 'did not contain sufficient information to complete the inclusion assessment'. Of these 11 sponsor-included studies, 8 were excluded by the EAC as their patient cohorts overlapped with those of the 3 studies subsequently accepted by the EAC.

1.3 Summary critique of clinical evidence submitted by the sponsor

The EAC considers that the sponsor included some of the relevant evidence on VTq and both comparators and considers that the sponsor's interpretation of the available clinical evidence was reasonable and provided a fair assessment of the studies submitted. Of the 11 studies provided by the sponsor, all fitted the required scope in terms of comparators and outcome

measures. The majority of these publications (mainly conference abstracts) provided limited study details, such as baseline characteristics of patients (e.g. ethnicity) and study design. However, the main problem identified is that many of these studies included overlapping patient populations, which is why the EAC subsequently rejected many of the sponsor included studies.

The EAC conducted its own systematic review to ensure that all available evidence had been considered. In doing so, five additional studies were identified and accepted by the EAC as fitting the scope and not including patient populations that overlapped with those of other studies. The EAC also performed its own meta-analysis to provide pooled estimates for prevalence, correlation, sensitivity and specificity of VTq and TE compared to liver biopsy. The results of the meta-analysis also contributed to the subsequent EAC economic model.

1.4 Summary of economic evidence submitted by the sponsor

The sponsor submitted the results of a search strategy combining terms related to the target condition (hepatitis), the intervention (VTq), and/or the comparator (TE) and economics. The sponsor found 5 studies related to the comparators but none related to the technology.

Since no economic evidence was available for the VTq technology, the sponsor submitted a cost model. The sponsor provided a decision tree model using 2013 prices from the National Health Service (NHS) and personal social services perspective to estimate the cost for VTq and the comparators. The sponsor reported a cost-saving of £10.31 per patient by using VTq compared to TE. On the other hand, and in comparison with liver biopsy the sponsor reported that VTq leads to a cost-savings of around £599.08 per patient.

1.5 Summary critique of economic evidence submitted by the sponsor

The EAC reviewed the sponsor’s search strategy and databases included and concluded that it could be improved in terms of the span and terms of the search. The EAC therefore undertook a new search for economic evidence

related to the technology and comparators and did not find any evidence on the technology. This substantiated the conclusions reached by the sponsor: that, presently, there is no economic evidence available for the technology.

The EAC considers that the proposed model generally addresses the scope issued by NICE, but nonetheless has important issues that need to be considered. Particularly, the model structure proposed by the sponsor neither: 1) reflects the clinical pathways for patients with fibrosis (both the current pathways with TE and liver biopsy and the proposed pathway with VTq); nor 2) takes into account all relevant costs and outcomes for diagnosing and treating liver fibrosis. On this basis, the EAC considered it necessary to remodel the sponsor's approach before any conclusion could be drawn.

1.6 External Assessment Centre commentary on the robustness of evidence submitted by the sponsor

All of the clinical evidence provided on VTq, TE and liver biopsy was based on published evidence, the majority of which took the form of conference abstracts. The submitted evidence included a mixture of study designs: retrospective/prospective, cross-over, observational and meta-analysis. Furthermore, many of the studies contained overlapping patient cohorts, therefore, the results could not be synthesised for the majority of the submitted evidence. All the submitted evidence used at least one of the comparators, TE or liver biopsy, with most studies including both, which is consistent with the scope.

1.7 Summary of any additional work carried out by the External Assessment Centre

The EAC conducted a systematic review of the clinical evidence, identifying 1131 abstracts. The review included liver diseases, liver fibrosis and cirrhosis, and hepatitis key words. The interventions included were VTq, ARFI, Fibroscan, TE and liver biopsy. The outcomes included were prognosis, predictive value of tests, receiver operating characteristic, adverse event, sensitivity, specificity, diagnostic accuracy, antiviral and quality of life. The search terms and strategy are presented in appendix 4. The search identified

10 studies (Kuroda, et al., 2010, Rizzo, et al., 2011, Chen, et al., 2012, Sporea, et al., 2012a, Ye, et al., 2012, Friedrich-Rust, et al., 2013, Friedrich-Rust, et al., 2014, Liu, et al., 2014, Nishikawa, et al., 2014, Yamada, et al., 2014); of which 3 had previously been identified by the sponsor as included studies (Sporea, et al., 2012a, Friedrich-Rust, et al., 2013, Friedrich-Rust, et al., 2014), and 2 had been excluded by the sponsor (Liu, et al., 2014, Yamada, et al., 2014). Outcome estimates from these studies were incorporated where possible into a meta-analysis to provide pooled estimates for correlation, sensitivity, specificity and prevalence for both VTq and TE in comparison to liver biopsy with the study populations of hepatitis B, hepatitis C or combined.

To address the issues related to the model submitted by the sponsor, the EAC remodelled the cost of VTq as compared to TE and liver biopsy. A short-term decision model based on the meta-analysis performed by the EAC was developed. Due to data limitations, the EAC also developed a sequential model, similar to the one submitted by the sponsor. In the model constructed by the EAC, patients with false negative and false positive results along with associated monitoring and/or treatment costs were also included in the decision model. The prevalence, sensitivity and specificity values used in the revised model were based on the meta-analyses performed by the EAC.

The revised model confirmed the overall cost conclusions reported by the sponsor i.e. the technology (VTq) generates cost savings when compared to TE and liver biopsy. The cost savings generated by the VTq strategy compared against liver biopsy were much larger than when compared to TE. Sensitivity analysis of the key variables also did not alter the cost saving conclusion for the technology (VTq) when compared against both comparators.

2. Background

2.1 Overview and critique of sponsor's description of clinical context

Virtual Touch Quantification (VTq) is a software application used with either the Acuson S2000 or the Acuson S3000 (Siemens Healthcare) ultrasound scanners to assess the stiffness of liver tissue. In the context of this assessment report, this is specifically in relation to liver fibrosis in patients with chronic hepatitis B or hepatitis C. Section 3 of the sponsor's submission contains the sponsor's critique of the clinical context for VTq. The EAC agrees with most of the sponsor's comments in this section, however there were several important details which the EAC considered to be absent.

The definitions of hepatitis and the Metavir score are presented in line with the scope. The sponsor describes the current methods of assessing liver fibrosis in these patients on page 15 of the submission. The sponsor refers to liver biopsy as the current gold standard (although it is acknowledged there are well documented limitations with this technique) and discusses the accuracy of elastography methods (VTq and TE) in comparison to liver biopsy.

The sponsor provides an estimate for the prevalence of hepatitis B and hepatitis C. The sponsor states 'The British Liver Trust currently reports the number of people in the UK with Hep B as 325,000' on page 16 of the submission. The British Liver Trust reference provided estimates that 1 in 350 people in the UK have chronic hepatitis B (Foster and Campbell, 2012)[iii]. Scaled to a UK population of 64 million (Statistics, 2014), this estimate would be equivalent to a figure of approximately 183,000 people in the UK with chronic hepatitis B. This figure is similar to estimates of the population size from the Department of Health (Health Protection Agency, 2006, Health Protection Agency, 2011) and the Foundation for Liver Research (Foundation for Liver Research, 2004). The figure of 325,000 comes from a report from the Hepatitis B Foundation UK (Pendleton and Wilson-Webb, 2007); however the EAC has also been provided with their newer report, published in 2013, which provides an estimate of 512,000 people with chronic hepatitis B (Desmond,

2013). The sponsor was unable to provide estimates for the proportion of patients within these categories who have liver fibrosis, or the distribution of Metavir scores within these patients. The EAC searched for this information, and is in agreement with the sponsor that this information is not currently available.

The sponsor provides two different estimates for the population of people with chronic hepatitis C in the UK: 255,000 and 215,000. The first figure, 255,000, is referenced to the British Liver Trust; however, the EAC has found this figure to be 400,000 after checking the original source material (Cramp, 2010)[iii]. The second figure, 215,000, is referenced to a report from Public Health England, and the EAC has been able to verify this figure (Harris, et al., 2013)[iv].

The EAC considers the populations suggested by the sponsor for the number of people with hepatitis B and hepatitis C to be reasonable.

Within the prevalence section, the sponsor states that 'injecting drug users account for 49% of cases in England'. The reference provided, a report from Public Health England, states that *"49% of PWID (people who inject drugs) tested positive for antibodies to HCV (hepatitis C)"* (Harris, et al., 2013). From this report, 90.3% of the people who test positive for hepatitis C have "injecting drug use" as a risk factor, much higher than the 49% stated.

The sponsor refers to NICE Clinical Guideline CG165 for the current clinical pathway for chronic hepatitis B (National Insitute for Health and Care Excellence, 2013). The sponsor presents issues of access to TE and risks associated with liver biopsy as current issues affecting clinical practice. The EAC has identified no other issues or uncertainties relating to current practice.

The current clinical pathway presented for chronic hepatitis C is brief and is not referenced. Additionally, no issues or uncertainties relating to or deviations from current clinical practice are discussed.

The new clinical pathways presented for chronic hepatitis B and C move the request for ultrasound elastography into primary care from secondary care.

The EAC considers that the potential algorithms presented are reasonable. The new pathways directly replace transient elastography in the current pathways with VTq, but the remainder of the pathways do not significantly change.

Expert advisers were approached to provide their comment on the clinical pathways presented. One expert adviser responded, stating that in people with hepatitis C, their personal experience was that in practice they found that fewer patients are now biopsied. It may be more likely to be performed in those who are not proceeding to treatment, or in those who have undergone treatment which has not been successful. In people with hepatitis B, necro-inflammation in the liver is not detected by stiffness measurements, and so other factors such as quantitative hepatitis B DNA levels are taken into account. They suggested this should be added to the model as these can affect the decision on treatment. It is noted that these tests would be added for both TE and VTq.

The section in the sponsor's submission on potential changes to the organisation and delivery of services relate to the benefits of ultrasound elastography over liver biopsy, and the benefits of VTq over TE. The EAC agrees with most of the points presented here. The EAC was uncertain about the final point (*'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'*), as it is not clear why VTq should allow earlier intervention as compared to TE. However the sponsor clarified that this statement was made on the basis that they believed that access to VTq would be easier than to TE (or liver biopsy). This is primarily because VTq is an 'add on' test to an existing procedure.

These changes to the organisation and delivery of services may allow the NHS to disinvest in other tests. The sponsor provides a brief list, which the EAC generally agrees with. The final statement discusses the number of patients who are 'no shows' for liver biopsy, and comments that they have not ascertained the actual proportion. The EAC queries what proportion of patients who are referred for liver biopsy are 'no shows', and whether this is a

significant number. Expert advisers were approached for their opinion. The responses received were <5%, one in every 30-40 appointments, around 10% and 10-15%. Comments were additionally made suggesting that the population demographics of the area may affect the level of 'no shows'.

The EAC considers the sponsor's description of the clinical context to be appropriate and relevant to the decision problem under consideration. The errors and omissions identified within the submission are minor.

2.2 Overview of sponsor's description of ongoing studies

The sponsor states that they have not been made aware of any ongoing studies. The EAC performed a search of the clinical trials database using the terms 'ARFI', 'VTq', 'Virtual Touch tissue quantification' and 'Acoustic Radiation Force Impulse' and identified the clinical trials presented in Table 2.1 which it considers may be relevant. Studies have been cross-referenced with all accepted and rejected studies found within the sponsor's systematic review and the additional systematic review performed by the EAC.

Table 2.1: Details of the ongoing clinical trials

Clinical Trials Identifier and current status	Title	Sponsor and Collaborators	Condition	Comparators	Brief summary
NCT01283230 On clinicaltrials.gov, study claims to have been completed but no papers, conference posters or presentation abstracts have been identified.	Evaluation of Liver Fibrosis Staging with Acoustic Radiation Force Impulse Elastography	Severance Hospital and Yonsei University, Seoul, Republic of Korea	Chronic liver disease including hepatitis B or hepatitis C, compared to healthy living liver and kidney donors	Not stated	This is a prospective observational cohort study. The aim is to identify the normal range of ARFI velocity and assess the best cut off values.
NCT02044523 This study is currently recruiting participants. Estimated primary completion date of July 2016.	Nonivasive staging of liver fibrosis: MR vs Ultrasound (ELF)	Centre Hospitalier de l'Université de Montréal, and Canadian Institutes of Health	hepatitis B, hepatitis C, Non-Alcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis	Liver biopsy	This is a case-only observational cross-sectional study. The aim is to compare the sensitivity of Fibroscan, ARFI and magnetic resonance

Clinical Trials Identifier and current status	Title	Sponsor and Collaborators	Condition	Comparators	Brief summary
		Research Montreal, Canada			elastography to histology results. The study will also examine diagnostic accuracy and influence of confounding factors such as iron deposition.
NCT01781208 This study is currently recruiting participants. Estimated primary completion date of November 2015.	Ultrasound Based Acoustic Radiation Force Impulse, Shear Wave Velocity Imaging in Pediatric Patients Undergoing Liver Biopsy	University of Michigan, Michigan, United States	Liver diseases which cause liver fibrosis and inflammation	Liver biopsy	This is a safety/efficacy study using a single group of patients. The aim is to evaluate the usefulness of the technique in diagnosing different liver conditions.

2.3 Critique of sponsor's definition of the decision problem

Population

The population is defined in the scope as *'adults or children with chronic hepatitis B or C in whom assessment of liver fibrosis is indicated'*.

All the sponsor's included studies have either been conducted in adults or do not provide the age range of the included patients. The scope includes children within its definition of the population.

Additionally, there were no full papers identified in the sponsor's systematic review which studied a paediatric population. One paper examining the use of VTq in paediatric patients has been identified within the EACs systematic review; however the final patient population in this paper (i.e. the population that undergoes VTq and has a liver biopsy) does not include any patients with viral hepatitis (Hanquinet, et al., 2013).

An additional meta-analysis was identified by the EAC within their systematic review (Guo, et al., 2014). This meta-analysis revealed one additional paper

with a paediatric population; however viral hepatitis was present in only 5 out of the 32 study entrants in the chronic liver disease study group (Noruegas, et al., 2012).

There is currently limited information on the use of VTq in children. It is noted, however, that one of the clinical trials included in Table 2.1 is being conducted in a paediatric population. The estimated primary completion date of this trial is November 2015, so additional data for this age group is likely to become available within the next two years.

Intervention

The technology described in the scope is the Virtual Touch Quantification (VTq) software application used with either the Acuson S2000 or S3000 ultrasound platforms.

All included studies except one used the Siemens Acuson S2000 ultrasound system to perform VTq imaging. The final study (Calvaruso, et al., 2010)[52], which was an abstract, did not specify which ultrasound scanner model was used. No clinical studies were submitted which provided evidence solely on the comparator technologies.

The sponsor provided 3 EC declarations of conformity. The date of the first CE mark for the Acuson S2000 was given as February 2008 in the submission, and the sponsor supplied the EC declaration of conformity from March 2008, and a second declaration from April 2012. The S3000 declaration of conformity is dated November 2012. Both ultrasound devices were classified as Class IIa medical devices. The sponsor's submission states that the Acuson S2000 and S3000 platforms are in compliance with ISO13485.

Comparator(s)

The comparators listed in the scope are transient elastography (TE) and liver biopsy. Table 2.2 lists the comparators and interventions for the studies included in the submission.

Table 2.2: Summary of study design, interventions and comparator for sponsor included clinical evidence.

EAC reference [sponsor reference]	Population	Technology/ Intervention	Comparator(2013)
Friedrich-Rust et al. (2014)[2]	hepatitis C	VTq	Transient Elastography, Liver Biopsy
Calvaruso et al. (2013)[8]	hepatitis C	VTq	Transient Elastography, Liver Biopsy
Aoki et al. (2013)[11]	chronic liver disease	VTq	Transient Elastography, Liver Biopsy
Atzori et al. (2013)[12]	hepatitis B, hepatitis C, Other	VTq	Transient Elastography, Liver Biopsy
Sporea et al. (2013d)[14]	hepatitis B, hepatitis C	VTq	Transient Elastography
Schneider et al. (2013)[17]	hepatitis B, hepatitis C	VTq	Transient Elastography, Liver Biopsy
Cassinotto et al. (2013b)[21]	hepatitis B, hepatitis C, Other	VTq	Transient Elastography, Liver Biopsy
Badea et al. (2013)[22]	hepatitis C	VTq	Transient Elastography, Liver Biopsy
Friedrich-Rust et al. (2013)[25]	hepatitis B	VTq	Transient Elastography, Liver Biopsy
Sporea et al. (2012a)[26]	hepatitis C	VTq	Transient Elastography, Liver Biopsy
Bota et al. (2012a)[31]	hepatitis B, hepatitis C, Other	VTq	Transient Elastography, Liver Biopsy
Le et al. (2012)[33]	hepatitis B, hepatitis C	VTq	Transient Elastography
Sporea et al. (2012e)[34]	hepatitis B, hepatitis C	VTq	Transient Elastography, Liver Biopsy
Sporea et al. (2012b)[38]	hepatitis C	VTq	Transient Elastography, Liver Biopsy
Friedrich-Rust et al. (2012b)[44]	mixed	VTq	Transient Elastography, Liver Biopsy
Karlas et al. (2011)[45]	hepatitis C, Other	VTq	Transient Elastography, Liver Biopsy
Sporea et al. (2011d)[47]	hepatitis C	VTq	Transient Elastography, Liver Biopsy
Calvaruso et al. (2010)[52]	hepatitis C	VTq	Transient Elastography, Liver Biopsy
Sporea et al. (2010d)[55]	hepatitis B, hepatitis C	VTq	Transient Elastography, Liver Biopsy
Lupsor et al. (2009)[61]	hepatitis C	VTq	Transient Elastography, Liver Biopsy
Lupsor et al. (2010) [57]	hepatitis C	VTq	Liver Biopsy
Sporea et al. (2011a)[48]	hepatitis C	VTq	Transient Elastography, Liver Biopsy
Bota et al. (2013a)[18]	mixed	VTq	Transient Elastography, Liver Biopsy

All sponsor-included studies use either one or both of the comparators listed in the scope. A full evaluation of the comparators used in the studies is included in section 3 of this report.

Outcomes

There are eight outcomes described in the final scope. The sponsor identifies three of these as secondary outcomes, and notes that the final outcome, device related adverse events, was reviewed separately.

The sponsor notes that the ‘correlation in assessment of stage of liver disease’ and ‘correlation in assessment of stage of fibrosis using Metavir score’ are equivalent as liver biopsy is the index test.

The EAC agrees with the sponsor’s opinion that three outcomes (use of anti-viral drugs, hospital bed usage and length of stay and requirement of liver biopsy) are secondary outcomes and are dependent upon the accuracy of VTq. A full review of the outcomes can be found in section 3 of the report.

Cost analysis

The cost analysis has assessed the impact of the technology (VTq) and comparators (TE and liver biopsy) in the patient population as specified by the scope. The EAC concludes that the sponsor has appropriately included the technology and comparators with regards to the cost analysis. The time horizon for the analysis is also sufficient to reflect differences in costs and consequences between the technology and comparators. This matches with the cost analysis specified in the scope. The EAC identified issues related to: 1) specific assumptions used in the model; and 2) the model structure.

Subgroups

There are no subgroups specified in the final scope.

Special considerations, including issues related to equality

There were no special considerations, including issues related to equality, specified in the final scope. The EAC has not identified any further equalities issues and the sponsor has not raised any new issues.

3. Clinical evidence

3.1 Critique of the sponsor's search strategy

The search strategy provided by the sponsor for VTq was based on:

- the target population: hepatitis B or hepatitis C
- the intervention: Acoustic Radiation Force Impulse (VTQ. [sic]) using Virtual Touch^{TM} Tissue Quantification (VTq)
- the comparators: Transient Elastography (Fibroscan) (TE) and the Index test (Liver Biopsy).

The sponsor used the same search criteria for both published and unpublished studies. Chronological limits were set between 2009 and 2014. The sponsor clarified through communication with the EAC (30th June 2014), that this time frame was selected as the first studies using VTq were published in 2009. This was confirmed by the EAC by cross-checking with the meta-analysis from Nierhoff et al. (2013)[viii] and the EAC's own systematic review (see section 3.9 below).

The sponsor's search identified 70 published studies of which 23 were considered relevant by the sponsor and were subjected to full-paper screening. The sponsor provided a flowchart of the study review process undertaken. Part of this review process included a subsection described as Siemens Clinical Abstracts. The EAC requested clarification of the process of obtaining these abstracts in correspondence dated 30th June 2014. The sponsor responded that the abstracts are *'collected by Siemens illustrating the use of the technology and that we would expect to be a fair appraisal of publications'.* Siemens Clinical abstracts are abstracts collected up to February 2013 on the ARFI technology for advertising purposes. No additional studies were identified from searches of clinical trial registries, and the sponsor did not identify any unpublished studies.

The sponsor included a total of 23 publications in their submission as potentially relevant for review. Of the 23 publications, the sponsor states that 12 are conference abstracts and '*did not contain sufficient information to complete the inclusion assessment'.* Of the remaining 11 publications that the sponsor did include for further evaluation, 10 were case-control observational studies (Lupsor, et al., 2009, Calvaruso, et al., 2010, Sporea, et al., 2010d, Karlas, et al., 2011, Sporea, et al., 2011a, Sporea, et al., 2011d, Sporea, et al., 2012a, Sporea, et al., 2012e, Friedrich-Rust, et al., 2013, Friedrich-Rust, et al., 2014)[2, 25, 26, 34, 45, 47, 48, 52, 55, 61] and 1 was a meta-analysis (Friedrich-Rust, et al., 2012b)[44].

Although not identified originally through the literature search (or included in the selected studies) the sponsor included the results of a further study (Yamada, et al., 2014)[xi] in Table B11 of their submission relating to the correlation between methods and patient mix. Correspondence between the EAC and the sponsor on 30th June 2014 sought clarification of the identification of this paper. The sponsor responded that this study *'was included to flag up the use of the technology in the follow up of patients undergoing antiviral therapy. This is to some extent a 'future use' but is probably something that should be considered.'* Therefore, the EAC has included this study as further identified clinical evidence and evaluates it in section 3.9.

The EAC notes that there are minor discrepancies in the description of the sponsor's systematic review methodology, such as incomplete search strategy search terms. Clarification was sought from the sponsor (dated 30th June 2014), who responded with the correct search terminology. The EAC also replicated the sponsor's search strategy and considers that it was lacking some important search terminology. Therefore, the EAC conducted a revised systematic review with additional search terms related to outcomes (see section 3.8) as defined in the scope.

3.2 Critique of the sponsor's study selection

The sponsor has included both abstracts and full publications in the systematic review. The EAC's literature review identified the full publications that correspond to some of the conference abstracts that the sponsor submitted. The same authors were identified in several of the included studies and several of the studies were identified as containing overlapping patient cohorts. This is discussed in further detail in section 3.3.

It is the EAC's opinion that the most comprehensive meta-analysis from Nierhoff et al. (2013)[viii] should have been included as clinical evidence as this included a higher number of studies. The sponsor identified this study in their search of DARE, but did not include it within their submission of clinical evidence.

3.3 Included and excluded studies

Table 3.1 provides a summary of all sponsor included published studies which the EAC accepted. Appendix 1 contains the EAC-rejected studies. All key findings from these studies are listed accordingly. The sponsor identified 23 studies, the majority of which are conference abstracts. Later in the submission, the sponsor restricts this to 11 accepted papers. However, as the sponsor has provided some assessment of all 23 papers, the EAC considered it to be prudent to review all of these sponsor-identified papers.

Sponsor-included studies:

- The mean age was reported in all studies using patient populations. This mean age ranged between 39 and 59 years. In one study by Karlas et al. (2011)[45] that included a healthy population as a subgroup the mean age was 27.8 years.

- The majority of the sponsor-submitted studies were conducted in European countries (n=15 studies). These included Germany, Netherlands, Romania, Italy, United Kingdom, France, and Austria.

Studies were also conducted in Japan and Vietnam. However, not all studies documented the study country clearly (n=4) (Lupsor, et al., 2010, Sporea, et al., 2010d, Bota, et al., 2012a, Sporea, et al., 2012b)[31, 38, 55, 57])

- The sample sizes ranged from 93 to 1,203 subjects.

Appendix 3 provides a summary of all 54 excluded studies. The EAC considers that the exclusion of 53 of these papers was appropriate. However, the EAC disagrees with the sponsor's exclusion of the following paper: Liu et al.(2014)[1]. In the sponsor's submission, the reason for excluding Liu et al was unclear. The EAC questioned the sponsor about this exclusion and, in response, the sponsor stated that the reason for excluding this study was that a copy of the paper could not be obtained (correspondence 30th June 2014). The sponsor further stated:

'I have looked at the paper as part of Section C and there is no reason not to include it in section B. My criticism is that it that they don't state the depth from the liver capsule from where they took their VTq measurements.' (Anthony Stephens, sponsor representative).

The EAC considers that Liu et al. (2014)[1] should not be excluded as the study population (hepatitis B), the index, the comparator, and the reference test all fulfil the inclusion criteria. Furthermore, the investigators performed validation of the results using a ten-fold cross-validation strategy. Therefore, the EAC has included this study as further identified clinical evidence and evaluated it in section 3.9.

In the case of Bota et al. (2013b)[16], the sponsor's rationale for exclusion is unclear. Bota et al. prospectively evaluated a proposed cut-off threshold showing very low negative predictive value for VTq. This study fulfils the inclusion criteria as listed in Table B1 of the sponsor's submission however outcome measurements are not provided, just measurements of positive predictive value and negative predictive value. Therefore the EAC agrees with the sponsor's exclusion of this study.

Table 3.1 contains a summary of the key points of the three sponsor-included studies, which the EAC also accepts. The key points of the remaining 20 studies are discussed in appendix 1. The EAC's decision to reject sponsor-included studies is summarised below.

The following are the 11 conference abstracts that did not contain enough information for full review at the time of the sponsor's submission. The tables containing the study design, reason for rejection and results can be found in appendices 1 and 2.

- Calvaruso et al. (2013)[8]: Acoustic radiation force impulse is better than transient elastography in assessing liver fibrosis in chronic hepatitis C using collagen proportionate area as reference.
- Aoki et al. (2013)[11]: Analysis of risk factors for aiming at early detection of hepatocellular carcinoma.
- Atzori et al. (2013)[12]: Non-invasive assessment of liver fibrosis: Acoustic radiation force impulse of the left lobe correlates best with ishak histology score.
- Sporea et al. (2013c)[14]: The feasibility of shear-wave elastographic methods for non-invasive assessment of liver fibrosis in chronic viral hepatitis patients.
- Schneider et al. (2013)[17]: Non-invasive assessment of liver fibrosis with acoustic radiation force imaging and transient elastography in chronic viral hepatitis.
- Cassinotto et al. (2013b)[21]: Assessment of liver fibrosis with VTQ: Comparison with M and XL probes of Fibroscan and FibroTest in chronic liver diseases.
- Badea et al. (2013)[22]: VTQ performance in the noninvasive assessment of HCV cirrhosis, compared to transient elastography and FIB score.
- Bota et al. (2012a)[31]: VTQ elastography vs. transient elastography: Which one is more influenced by high aminotransferases values.

- Le et al. (2012)[33]: Comparison of liver stiffness values by virtual touch VTQ and Fibroscan TE in large sample study of 554 cases.
- Sporea et al. (2012b)[38]: Which elastographic method (transient elastography or VTQ) is more useful for liver fibrosis evaluation in patients with chronic hepatitis C? An international multicenter study.
- Lupsor et al. (2009)[57]: Performance of Acoustic Radiation Force Impulse imaging in the noninvasive assessment of liver fibrosis in comparison to unidimensional transient elastography.

The sponsor stated that they *'have not included any studies which were obvious duplicates'*. They state they expected that the meta-analysis by Bota et al. (2013a)[18] was one of the papers which included data which had been previously reported.

Of the 11 sponsor-accepted studies (of which all fit the scope), the EAC determined the following 8 studies to have overlapping cohorts and subsequently excluded them from further review. The tables containing the study design, reason for rejection and results can be found in appendices 1 and 2.

- Sporea et al. (2012e)[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.
- Friedrich-Rust et al. (2012b)[44]: Performance of Acoustic Radiation Force Impulse imaging for the staging of liver fibrosis: A pooled meta-analysis.
- Karlas et al. (2011)[45]: Acoustic radiation force impulse imaging (VTQ) for non-invasive detection of liver fibrosis: Examination standards and evaluation of interlobe differences in healthy subjects and chronic liver disease.
- Sporea et al. (2011d)[47]: Is it better to use two elastographic methods for liver fibrosis assessment?

- Sporea et al. (2011a)[48]: How efficient is acoustic radiation force impulse elastography for the evaluation of liver stiffness?
- Calvaruso et al. (2010)[52]: Comparison of transient elastography (TE) and acoustic radiation force impulse (ARFI) for noninvasive staging of liver fibrosis in patients with chronic hepatitis C.
- Sporea et al. (2010d)[55]: Which is the best noninvasive ultrasound method for the evaluation of liver fibrosis?
- Lupsor et al. (2009)[61]: Performance of a new elastographic method (ARFI technology) compared to unidimensional transient elastography in the noninvasive assessment of chronic hepatitis C. Preliminary results.

Table 3.1: Summary of key points from sponsor-included published studies which the EAC accepts

EAC reference [sponsor reference]	Study	Patient population	Intervention and/or Comparator	Country	Age/gender	Study design	Comments/critique of study
Friedrich-Rust et al. (2014)[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.	hepatitis C (n=253)	VTq vs TE, LB	Germany, Netherlands, Romania	NA	Cross-over; International multicentre study.	CIs reported. Study aim/hypothesis addressed. Abstract. **Sponsor identified and included.** **EAC accepted.**
Freidrich-Rust et al. (2013)[25]	Acoustic radiation force impulse imaging for non-invasive assessment of liver fibrosis in chronic hepatitis B.	hepatitis B (n=114)	VTq vs TE, LB	Germany, Netherlands	39 years ±12 Male: 77 (67%)	Prospective, cohort, multi-centre study.	ROC curves used for comparisons at different levels of severity based on histology (liver fibrosis). Aims addressed. CIs calculated. Full paper. **Sponsor identified and included.** **EAC accepted.**
Sporea et al. (2012a)[26]	Acoustic Radiation Force Impulse Elastography for fibrosis evaluation in patients with chronic hepatitis C: An international multicenter study.	hepatitis C (n=914), 911 valid cases.	VTq vs TE, LB	Japan, Romania, Germany, Italy, Austria	55.7 ± 13.1 Male n=423 (46.3%)	Retrospective cohort, multicentre study.	Correlation used to assess reliability, using Spearman test. No CIs. Hypothesis was not accurately tested. A subgroup of 400 patient with chronic Hepatitis C assessed by ARFI and TE. Full paper. **Sponsor identified and included.** **EAC accepted.**

3.4 Overview of methodologies of all included studies

The sponsor identified studies all used the same comparator (VTq), but with varying study designs and study populations. The EAC considered the entire 23 sponsor identified studies that were submitted and reviewed the methodologies.

VTq studies identified by the sponsor (n=23):

- The studies employed a mixture of designs: retrospective/prospective cross-over, observational cohort and meta-analysis. There were no RCT studies. The studies were a mixture of single or mixed centre studies or meta-analyses.

- In all the submitted evidence, the studies used the intervention as specified in the scope: *'the Virtual Touch Quantification (VTq) software application used with the Siemens Virtual Touch Tissue Imaging systems (the Acuson S2000 or S3000 ultrasound platforms)'*.

- The studies all used either the comparator TE or Liver Biopsy, with most studies including both of these comparators. This is consistent with the comparators specified in the scope (described further in section 3.6).

- The studies were performed on both healthy and patient populations. Nine studies included patient populations of hepatitis B and/or C. The remaining studies consisted of a mixture of study subjects with hepatitis B, hepatitis C, chronic liver disease, chronic viral hepatitis, non-viral hepatitis, hepatitis C and/or hepatitis B, as well as healthy volunteers in some cases. The patient population defined in the scope is: '*adults or children with chronic hepatitis B or hepatitis C in whom assessment of liver fibrosis is indicated'*. Therefore, the EAC considers that all studies included patient populations that are specified in the scope.

- Several of the studies documented confidence intervals within the text. Those that did not report confidence intervals were predominantly conference abstracts later rejected by the sponsor. Of note, these were not rejected due to lack of reported confidence intervals, but due to overlapping patient cohorts (as described in section 3.3).
- The majority of the studies were abstracts and not full publications.
- Several of the studies also failed to detail adequately baseline characteristics of the study populations. Similar to the documentation of confidence intervals, this lack of detail featured predominately in the conference abstracts.

3.5 Overview and critique of the sponsor's critical appraisal

The sponsor conducted a critical appraisal of only eleven studies that were identified in their systematic review and internal searches and subsequently accepted by the sponsor. The sponsor states that they only assessed studies that: *'were diagnostic test accuracy (DTA) studies and the results extracted from these studies were unit of analysis (patient or lesion); AUROC value for different states of fibrosis (Metavir) score for F0, F1..F4.'*

The critical appraisal of the studies provided limited information on potential bias. For all eleven studies, 'n/a' was recorded for both 'minimise bias' and 'outcome minimise bias'. The sponsor has confirmed that in this situation 'n/a' has been used to imply not available, rather than not applicable. There is no discussion of methods used to minimise bias, or whether the reported outcomes contributed to bias minimisation.

In 8 out of the 11 studies, the identified confounding factors are presented as the stages of liver fibrosis (F0-F4). The sponsor did not elaborate in what way the liver fibrosis stages were confounding factors. In the remaining studies, the sponsor responded 'yes' to this question with no further details provided as to what the identified confounding factors were.

The sponsor stated that the confounding factors were not accounted for in 6 of the 11 studies, and that the information required to decide whether the confounding factors had been suitably accounted for was not present in 3 studies. Sporea et al. (2012a)[26] reported that they accounted for differences between Asian and European populations, although no information was provided as to how this was taken into account, and these populations were not listed in the box 'identifying confounding factors'. Lupsor et al. (2009)[61] identified a study bias within this box (selection bias): *'uneven distribution of fibrosis stages and overrepresentation of patients with severe fibrosis-cirrhosis'.*

3.6 Results

In Table 3.2, the EAC provides a summary of the outcomes of all sponsor-identified studies that the EAC also agrees should be included. Appendix 2 contains the studies, which the EAC has rejected. All of the sponsor-identified studies were considered by the EAC to contain comparators and outcomes that fitted within the scope.

Of the original 23 sponsor-identified papers, the sponsor stated that '*12 were reported as conference abstracts, did not contain sufficient information to complete the inclusion assessment'*. The sponsor also stated that *'time constraints have prevented us from contacting the authors of papers when there was insufficient information for full assessment'.* Given this, the EAC has reviewed all 23 papers (as detailed in Table 3.1 and 3.2 and appendices 1 and 2). The EAC agrees with the sponsor's rationale for excluding the 12 conference abstracts from further review in the submission.

The following are the remaining sponsor-accepted studies that the EAC includes as they fit the specified scope, provide sufficient information, and do not have overlapping cohorts:

- Friedrich-Rust et al. (2014)[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.

- Freidrich-Rust et al. (2013)[25]: Acoustic radiation force impulse imaging for non-invasive assessment of liver fibrosis in chronic hepatitis B.
- Sporea et al. (2012a)[26]: Acoustic Radiation Force Impulse Elastography for fibrosis evaluation in patients with chronic hepatitis C: An international multicenter study.

The EAC also makes the following comments regarding the 3 EAC-accepted sponsor-identified papers:

- All 3 papers assess correlation in assessment of stage of liver disease and/or fibrosis using Metavir score. Friedrich-Rust et al. (2014)[2] found a significant correlation between VTq and TE with histological fibrosis stage. Whilst Sporea et al. (2012a)[26] found no significant overall correlation; a highly significant correlation was found between VTq and liver fibrosis stage (Spearman $r=0.65$, $p<0.001$). All three papers included the outcome measure of correlation in assessment of stage of fibrosis using the Metavir score. Statistically significant correlations were found for histological fibrosis stages between TE and VTq.

- All 3 studies assessed liver fibrosis using AUROC.

    - Friedrich-Rust et al. (2014)[2] compared the AUROC values of both VTq vs TE (intention to diagnose) and VTq vs TE (per protocol). The only significant comparison was VTq vs TE (intention to diagnose) $F \geq 2$ ($p=0.03$).

    - Friedrich-Rust et al. (2013)[25] documented sensitivity and specificity values using AUROC for fibrosis stage with confidence intervals. When comparing VTq to TE, they found

no significant difference for either intention to diagnose or per protocol between TE and VTq.

  - Sporea et al. (2012a)[26] concluded that TE was significantly better than VTq for predicting presence of liver cirrhosis (p=0.01) and fibrosis (p=0.01). No significant difference was found for predicting severe fibrosis.

- None of the papers document the following outcome measures (as specified in the scope).
  - Correlation in assessment of stage of fibrosis using Metavir score.
  - Use of anti-viral drugs.
  - Quality of life measures.
  - Hospital bed usage.
  - Length of stay.
  - Requirement for liver biopsy.
  - Device-related adverse events.

Table 3.2 presents the outcome measures from the 3 studies accepted by the EAC. The outcome measures from the remaining sponsor-included studies can be found in appendix 2.

Table 3.2: Summary of outcomes from sponsor identified studies which the EAC also accepts. 'NA' = not available

EAC reference [sponsor reference]	Study	Subjects	Correlation in assessment of stage of liver disease and/or fibrosis using Metavir score	Sensitivity and specificity (using AUROC) in assessment of liver fibrosis	1) Use of anti-viral drugs 2) Requirement for liver biopsy	Quality of life measures	1) Hospital bed usage 2) Length of Stay	Device-related adverse events
Friedrich-Rust et al. (2014)[2] **Sponsor identified and included. EAC accepted.**	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	253 patients with chronic hepatitis C. Prospectively assessed for VTq, TE and blood tests. Liver histology was staged by a central pathologist and used as reference.	VTq and TE correlated significantly with histological fibrosis stage. No significant difference was found between TE and VTq for the diagnosis of F ≥ 2 (p=0.15), F≥3 (p=0.11) and F=4 (p=0.19).	AUROC (95% CI) of VTq vs TE (intention to diagnose n=247): F≥1: 0.69 (0.60-0.79) vs 0.76 (0.70-0.83) (p=0.21) F≥2: 0.77 (0.71-0.83) vs 0.85 (0.80-0.89) (p=0.032) F≥3: 0.83 (0.77-0.89) vs 0.88 (0.83- 0.93) (p=0.15) F=4: 0.84 (0.77- 0.91) vs 0.89 (0.84-0.95) (p=0.18). AUROC (95% CI) of VTq vs TE (per protocol n=182): F≥1: 0.75 (0.67-0.83) vs 0.80 (0.72-0.88) (p=0.28) F≥2: 0.81 (0.74-0.88) vs 0.85 (0.80-0.91) (p=0.15) F≥3: 0.88 (0.82-0.94) vs 0.92 (0.89- 0.97) (p=0.11) F=4: 0.89 (0.83- 0.96) vs 0.94 (0.90-0.98) (p=0.19).	NA	NA	NA	NA
Freidrich-Rust et al. (2013)[25] **Sponsor identified and included. EAC accepted.**	Acoustic radiation force impulse imaging for non-invasive assessment of liver fibrosis in chronic hepatitis B.	114 patients, n=92 with valid VTq, n=92 used for the ITT analysis and n=88 (due to failure of four TE) in the per protocol analysis. Ten valid measurements performed.	The Spearman correlation coefficient between ARFI imaging and TE with the histological fibrosis-stage was significant with correlations of r=0.415 (p<0,0001) and r=0.556 (p<0,0001) for VTq & TE respectively.	AUROC (95% CI) for fibrosis stage for ARFI (n=114): F≥1: 0.66 (0.55- 0.78) F≥2: 0.73 (0.61- 0.85) F≥2adj: 0.79 (0.67- 0.91) F≥3: 0.94 (0.88-0.997) F≥4 0.97 (0.93- 1.00). TE (per protocol, n=88): F≥1: 0.78 (0.68-0.88) F≥2: 0.82 (0.70-0.93) F≥2adj: 0.88 (0.76-0.99) F≥3: 0.94 (0.88-0.99) F≥4: 0.94 (0.86-1.00). ARFI (n=88): F≥1: 0.66 (0.55-0.78) F≥2: 0.74 (0.60-0.88) F≥2adj: 0.80 (0.66-0.94) F≥3: 0.92 (0.84-1.00) F≥4: 0.98 (0.94-1.00). TE (intention to diagnose, n=92): F≥1: 0.78 (0.67-0.87) F≥2: 0.84 (0.72-0.93) F≥2adj: 0.89 (0.78-0.99)	NA	NA	NA	NA

EAC reference [sponsor reference]	Study	Subjects	Correlation in assessment of stage of liver disease and/or fibrosis using Metavir score	Sensitivity and specificity (using AUROC) in assessment of liver fibrosis	1) Use of anti-viral drugs 2) Requirement for liver biopsy	Quality of life measures	1) Hospital bed usage 2) Length of Stay	Device-related adverse events
				F≥3: 0.95 (0.90-1.00) F≥4: 0.94 (0.86-1.00). ARFI (n= 92): F≥1: 0.67 (0.55-0.77) F≥2: 0.76 (0.62-0.89) F≥2adj: 0.82 (0.68-0.95) F≥3: 0.94 (0.86-1.00) F≥4: 0.98 (0.93-1.00). ARFI and TE were compared on n=92 patients (Intention to diagnose) and on n=88 patients (per protocol), no differences were found to be significant at the 5% level. Further analysis was done for ARFI. On the basis of exclusion of F≥2 and diagnosis of F≥2: Cut-off (m/s): 1.03 and 1.39 respectively. Sensitivity 91% (75%- 98%) and 50% (32%- 68%). Specificity 26% (17%- 36%) and 90% (82%- 96%).				
Sporea et al. (2012a)[26] **Sponsor identified and included. EAC accepted.**	Acoustic Radiation Force Impulse Elastography for fibrosis evaluation in patients with chronic hepatitis C: An international multicenter study.	hepatitis C n= 914 VTq vs LB, all patients. VTq vs TE vs LB, a subgroup of n=400 patients. Ten valid measurements.	AFRI & Liver fibrosis stage: highly significant correlation (Spearman r=0.654, p<0.0001) The overall correlation with histological fibrosis was not significantly different for TE in comparison with ARFI. Correlation of TE & AFRI with LB: The overall correlation with histological fibrosis was similar for both methods: TE: r=0.728 (p<0.0001) vs ARFI r=0.689 (p<0.0001).	AFRI & LB values (Fibrosis stage, cut-off [m/s], AUROC, sensitivity, specificity) were: F≥1 (>1.19): 0.779; 69.9; 80 F≥2 (>1.33): 0.792; 69.1; 79.8 F≥3 (>1.43): 0.829; 74.8; 81.5 F=4 (>1.55): 0.842; 84.3; 76.3. TE was better than AFRI: for predicting the presence of liver cirrhosis (AUROC: 0.932 vs 0.885, p=0.01) and fibrosis (AUROC: 0.857 vs 0.772, p=0.01); while for predicting significant and severe fibrosis the two elastographic methods had similar values: AUROC: 0.818 vs 0.813, (p=0.77) and AUROC: 0.866 vs 0.862 (p=0.81).	NA	NA	NA	NA

3.7 Description of the adverse events reported by the sponsor

The sponsor reports no adverse events in the submission. The EAC has repeated the sponsor's systematic review and searched all included and excluded studies from the assessment report as well as the studies that the EAC identified in the additional systematic review. No adverse events have been identified in the literature. Two papers, (Sporea, et al., 2011a)[48] and (Sporea, et al., 2010a)[60], contain the claim that the technology is "totally free of adverse events".

The sponsor states in the submission that *'adverse events associated with liver biopsy are well described'*. The reference provided (Bravo, Sheth and Chopra, 2001) presents a comprehensive list of potential adverse events or complications associated with a liver biopsy.

The EAC does not have any concerns related to adverse events with this technology. The expert advisers were asked if they had any knowledge of adverse events which had occurred previously or could potentially occur in the future. No expert adviser responded with any known or potential adverse events related to this technology. One expert adviser commented that it should not be used on a developing fetus, and that some concerns had been raised over smaller vulnerable structures, such as the retina, but so far there is no evidence available to support these concerns.

3.8 Description and critique of evidence synthesis and meta-analysis carried out by the sponsor

The sponsor provided a brief synthesis of evidence in their submission:

- The submitted clinical evidence lacked information on patient preference or adverse events.
- The sponsor summarised the results of relevant studies by population subgroups (hepatitis B, hepatitis C and Other) and comparator tests (TE and liver biopsy when applicable).

- The sponsor identified two relevant systematic reviews: Bota et al. (2013a)[18] and Nierhoff et al. (2013)[viii]. The sponsor describes the outcomes of these two meta-analyses. The sponsor notes that Bota et al. did not differentiate between patient populations.

- The sponsor adequately describes how the available evidence was synthesised in Table B11 and the reasoning for the subgroup breakdowns.

- In Table B11, the sponsor documents Metavir scores and patient mix for 11 studies and summarises the main findings:

    - The sponsor interpreted the differing correlation between varying Metavir score and VTq.

    - The sponsor highlighted that not all studies assessed diagnostic and prognostic accuracy, or AUROC values.

    - Some studies also did not define their patient population mix adequately (i.e. whether hepatitis B or hepatitis C patients) or were weighted towards one particular patient population type.

- In Table B12, the sponsor documents AUROC values for VTq and TE for 13 studies and summarises the main findings:

    - The sponsor describes the difficulty in assessing mean scores for AUROC values, and considers it *'inappropriate as the data is not normally distributed'.*

    - The sponsor also notes the difficulty in assessing the results with the differing and undefined population groups.

The sponsor summarises by concluding from the qualitative synthesis of the studies, *'VTq 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'*. The EAC notes that this is plausible; however, the sponsor does not conduct a meta-analysis, which might have provided more weight

to this assertion. The EAC does note that the lack of population specification in some of the sponsor-identified studies would make this difficult.

The sponsor provided an interpretation of the clinical evidence. They stated that *'VTq can be used in clinical practise 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)*.' The sponsor summarised the clinical evidence that they provided in their submission. Under 'strengths' the sponsor highlighted that the studies were *'straightforward, easy to interpret and provided a quantitative answer*'. Under 'limitations', the sponsor listed the issues around mixed populations (Hepatitis B and C), the outcome measures, issues around subgroup analysis (i.e. ethnicity), unclear fibrosis stages listed and lack of information regarding follow-up. The EAC considers that this interpretation of the evidence (in terms of the sponsor submitted evidence) is reasonable and provides a fair assessment of the studies strengths and limitations.

3.9 Additional work carried out by the External Assessment Centre in relation to clinical evidence

The EAC had the following concerns regarding the effectiveness of the sponsor's study selection:

- Although the search terms and time limits used by the sponsor are representative of the technology, a large proportion of the published studies are using overlapping cohorts.
- Identifying which studies are using independent groups of patients is challenging. This was noted in the sponsor's submission and during the clinical evidence submission discussion teleconference held on the 30th June 2014.
- The EAC decided that this should be addressed by conducting an additional systematic review to ensure that all available evidence had been considered.

Table 3.3 lists the revised EAC systematic review search terms. The search strategy used is presented in appendix 4.

Table 3.3: Selection criteria used to identify relevant published studies.

Inclusion criteria	
Population	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)
Outcomes	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 Use of anti-viral drugs Quality of life measures Hospital bed usage and length of stay Requirement for liver biopsy Device-related adverse events
Study design	Diagnostic accuracy studies
Language restrictions	• English language only • Foreign language papers with English abstracts could be included
Search dates	2009 – Current
Exclusion criteria	
Population	Mixed patient cohort, use of a fibrosis score other than Metavir, overlapping cohorts with other identified populations
Study design	Case studies, editorials, letters, reviews
Interventions	No restriction

A total of 49 studies were selected for full paper review, of which 39 were rejected for reasons detailed in Appendix 5. Of the 10 studies that the EAC's systematic review identified as relevant in terms of the scope, 3 were also identified in the sponsor's own systematic review: Friedrich-Rust et al. (2014)[2], Friedrich-Rust et al. (2013)[25] and Sporea et al. (2012a)[26]. The findings of the remaining 7 EAC-accepted papers and an overview of each study are presented below in Table 3.4.

It is noted here that 2 of the studies, (Liu, et al., 2014) and (Yamada, et al., 2014), were previously identified by the sponsor, but were not included in their final selection. Figure 3.1 shows a PRISMA flow diagram including both the sponsor's and the EAC's search strategy.

Figure 3.1: PRISMA flow diagram showing the sponsor's search (dotted box) and the EAC search results

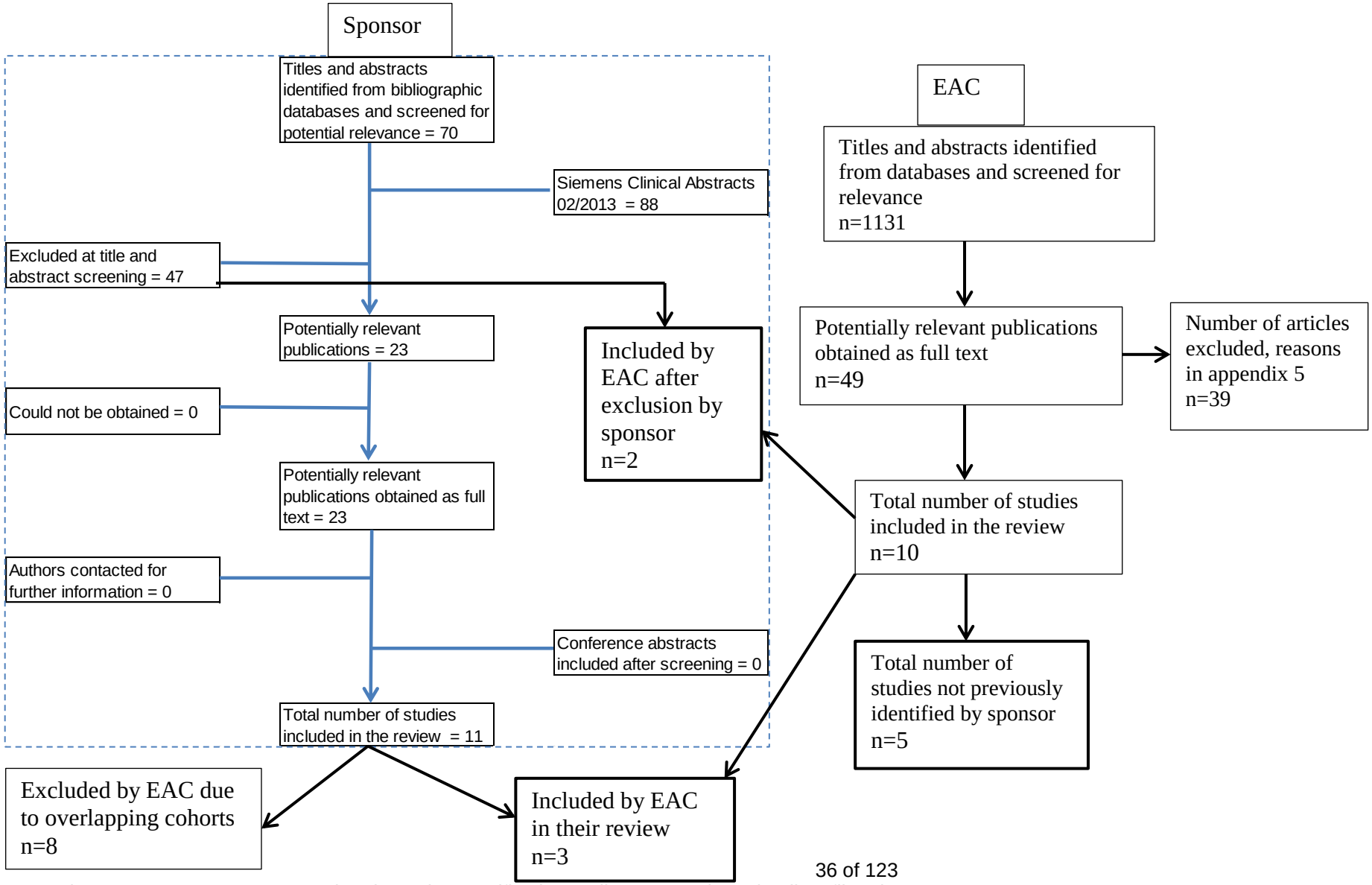


Table 3.4: Summary of key points from additional accepted EAC systematic review studies (n=7).

EAC reference	Study	Patient population	Intervention and/or Comparator	Country	Age/gender	Study design	Outcomes
Chen et al. (2012)	Effects of patient factors on noninvasive liver stiffness measurement using acoustic radiation force impulse elastography in patients with chronic hepatitis C.	Patients with hepatitis C (n=127).	VTq, liver biopsy	Taiwan/China	Mean age 51.6 years. Male/female = 51/58.	Prospective, observational, operator-blind study, liver biopsy within one hour of ARFI measurements (Acuson S2000). No follow up.	Spearman's rank cc = 0.696 (p<0.001). AUROCs (CI) were: F1 vs. F2-F4 = 0.847 (0.779-0.914), F1-2 vs. F3-4 = 0.902(0.835-0.97), F1-3 vs. F4 = 0.831(0.723-0.939).
Kuroda et al. (2010)	Non-invasive evaluation of liver fibrosis using acoustic radiation force impulse imaging in chronic hepatitis patients with hepatitis C virus infection.	N=30 patients with hepatitis C, n=30 patients with liver cirrhosis, and n=10 healthy subjects (controls)	VTq, biochemical tests, liver biopsy	Japan	Mean age (SD) 65.5 (6.5) years Male/female = 13/17	Prospective, diagnostic accuracy study Biochemical tests performed on the same day as ARFI measurements. Timing of liver biopsy unclear.	Mean shear wave velocity values: F0-1: 1.09±0.22m/s F2: 1.24±0.52m/s F3: 1.61±0.79m/s F4: 2.35±1.11m/s Diagnosis of liver cirrhosis using ARFI: AUROC: 0.930 (no CI). The most appropriate cut off value for shear wave velocity values was 1.59 (sensitivity 95%, specificity 83%)

EAC reference	Study	Patient population	Intervention and/or Comparator	Country	Age/gender	Study design	Outcomes
Liu et al. (2014)[1]	Optimal linear combination of ARFI, transient elastography and APRI for the assessment of fibrosis in chronic hepatitis B.	Patients with hepatitis B (n=95) and 16 healthy volunteers.	VTq, liver biopsy, TE.	China	Patients with hepatitis B (mean age 40.8 years, range 21-62), healthy volunteers (mean age 3 years, range 24-67). Male/female = 81/30.	Prospective, Diagnostic accuracy, ARFI measurement with Siemens Acuson S2000 within one day of liver biopsy. No follow up.	AUROCs, ARFI F≥2 0.91 (p=0.27), F4: 0.96 (p=0.04), TE F≥2: 0.87 (p=0.04), F4: 0.96 (p=0.13).
Nishikawa et al. (2014)	Factors correlating with acoustic radiation force impulse elastography in chronic hepatitis C.	Patients with hepatitis C (n=108).	VTq, liver biopsy.	Japan	Mean age 59.5 years (range 49.0-66.0). Male/female = 56/52.	Prospective diagnostic accuracy, ARFI measurement with Siemens Acuson S2000 within one week of liver biopsy. Patients' underwent a liver biopsy before starting treatment with interferon. No follow up.	Shear velocity value was significantly correlated with fibrosis stage r=0.732 (p<0.0001). AUROC: F1: 0.81, F2: 0.9, F3: 0.86, F4: 0.88.

EAC reference	Study	Patient population	Intervention and/or Comparator	Country	Age/gender	Study design	Outcomes
Rizzo et al. (2011)	Comparison of Transient Elastography and Acoustic Radiation Force Impulse for Non-Invasive Staging of Liver Fibrosis in Patients With Chronic Hepatitis C.	Patients with hepatitis C (n=139).	VTq, liver biopsy, TE.	Italy	Mean age 55.0 years. Male/female = 83/56.	Prospective, diagnostic accuracy, percutaneous liver biopsy and ARFI/TE measurements (Acuson S2000) within 6 months. No follow up.	ARFI AUROCs (CI) were: F>2 = 0.86 (0.79-0.91), F>3 = 0.94 (0.89-0.97), F>4 = 0.89 (0.83-0.94). TE AUROCs (CI) were: F>2 = 0.78 (0.70-0.85), F>3 = 0.83 (0.75-0.89), F>4 = 0.80 (0.72-0.86).
Yamada et al. (2014)[xi]	Significance of liver stiffness measurement by acoustic radiation force impulse (ARFI) among hepatitis C patients.	Patients with hepatitis C (n=124).	VTq. peg-IFN plus ribavirin combination therapy Liver fibrosis assessed histologically by liver biopsy, Response to treatment measured with serum hepatitis C RNA levels and ARFI.	Japan	Mean age 57.0 years. Male/female = 56/94.	Diagnostic accuracy and Prediction of response to treatment, Prospective status not clear, ARFI measurement (Acuson S2000) was performed within one week preceding liver biopsy. Follow up was at weeks 4, 12, 24, 36, 48, end of treatment and week 24 after the treatment for genotype 1. For genotype 2 follow-up was at weeks 4, 12, 24, and week 24 after the treatment.	The shear velocity value increased with the progression of the histological fibrosis stage, as assessed using the Metavir scoring system and a significant correlation was found between the two variables (Pearson product–moment correlation coefficient = 0.764 (p<0.001). The AUROCs were F≥2 (0.890), F≥3 (0.943),

EAC reference	Study	Patient population	Intervention and/or Comparator	Country	Age/gender	Study design	Outcomes
Ye et al. (2012)	Liver and Spleen Stiffness Measured by Acoustic Radiation Force Impulse Elastography for Noninvasive Assessment of Liver Fibrosis and Esophageal Varices in patients with chronic hepatitis B.	Patients with hepatitis B n=204) and n=60 healthy volunteers, Only 66 out of 204 patients underwent liver biopsy for comparison with ARFI.	VTq, ultrasound guided liver biopsy.	China	Patients with hepatitis B (mean age 35.5 years, range 19-63), healthy volunteers (mean age 30 years, range 20-54). Male/female = 158/106	Prospective diagnostic accuracy, ARFI measurement with Siemens Acuson S2000 within three days of liver biopsy. No follow up.	Spearman's rank cc = 0.87 (p<0.001). AUROCs (CI) were: F0-2 vs. F3 = 0.99, F0-2 vs. F4 = 0.97.

Two of the included studies examined the diagnostic accuracy of VTq in patients with hepatitis B (Ye, et al., 2012, Liu, et al., 2014)[1], and five studies did so in patients with hepatitis C (Kuroda, et al., 2010, Rizzo, et al., 2011, Chen, et al., 2012, Nishikawa, et al., 2014, Yamada, et al., 2014)[xi]. All the identified studies used Acuson S2000 for the ARFI measurements. Rizzo et al. and Liu et al. investigated both comparators (liver biopsy and TE) and the remaining 5 studies compared ARFI measurements only with the gold standard of liver biopsy.

Yamada et al. (2014)[xi] investigated both the diagnostic accuracy of ARFI and its ability to predict response to therapy with antiviral treatment. The n=124 patients with chronic hepatitis C enrolled in this study consisted of n=94 with hepatitis C genotype 1 and n=40 with moderate fibrosis (Metavir fibrosis score F2). Of these patients, n=61 received pegylated interferon (peg-IFN) plus ribavirin combination therapy, and the treatment responses were assessed. The shear velocity value measured by ARFI could not predict the treatment response for patients with hepatitis C genotype 2 but showed some benefit for patients with genotype 1.

In the study by Nishikawa et al. (2014), ARFI elastography was performed in n=108 consecutive patients with hepatitis C who underwent liver biopsy. The results showed that ARFI correlated significantly with liver fibrosis stage in all patients. Additionally, ARFI correlated significantly with body mass index (BMI), γ-glutamyltranspeptidase (GTP) and hyaluronic acid blood levels in fibrosis stages F0-1, F2 and F3-4 respectively. ARFI measurements did not correlate with inflammation.

Contrary to the findings of Nishikawa et al. (2014), the study by Chen et al.(2012) found that although there was a statistically significant correlation ($r=0.70$, $p<0.001$) (with all AUROCs values above 0.83) between ARFI and liver biopsy, the degree of concurrent hepatic necro-inflammatory activity significantly affected the measurements of liver fibrosis using ARFI.

Both Liu et al. (2014)[1] and Ye et al. (2012) investigated the diagnostic accuracy of ARFI in patients with hepatitis B and healthy volunteers. In Ye et al., among the n=204 patients, only n=66 underwent liver biopsy while in Liu et al. all n=95 patients underwent liver biopsy. In Liu et al., both ARFI and TE had similar AUROCs values for both the intermediate (F2) and advanced (F4) fibrosis stages. In Ye et al., ARFI liver stiffness measurements showed good correlation with the fibrosis stage ($p = 0.87$, $p<0.001$), and a high diagnostic accuracy between early/intermediate and advanced fibrosis stages (F0-2 vs. F3 = 0.99, F0-2 vs. F4 = 0.97).

In the study by Rizzo et al. (2011), ARFI imaging was found to be reproducible and accurate for staging of both intermediate (>F2) and advanced (F3-F4) liver fibrosis in a cohort of n=139 consecutive patients with hepatitis C. The AUROC results for these stages were comparable with the performance of TE.

Meta-analysis

The included studies were reviewed and population outcome data were extracted (Tables 3.5 and 3.6). Where actual frequencies were not reported in fully in the papers they were calculated using available study summary data (sensitivity, specificity, totals). Random effects meta analyses were used to calculate all pooled proportions for correlation, sensitivity, specificity, and prevalence. Prior to analysis the proportions were transformed using the logit function (log[p/(1-p)]) as in most cases they were either close to 0 or close to 100% and so skewed. For positive skewness (log[p/(1-p)]) was used and (log[(1-p)/p]) for negative skewness. For sets of proportions that had a wide range, ie some high and some low values, no transformation was used prior to pooling. Numerator values of ‘0’ (only in specificity) were replaced with ‘0.5’ to permit pooling. Results of meta analyses were back-transformed to the natural scale as appropriate to give estimated pooled proportions and 95% confidence intervals. All analyses were conducted using Stata v11.0. The ‘metan’ procedure was used for the random effects meta analyses.

Pooled values were calculated for each study population (i.e. hepatitis B, hepatitis C and combined) and then for the liver fibrosis comparator (i.e. VTq and TE) to liver biopsy for all liver fibrosis stages (where available). In cases where only a single study was available, the appropriate proportion and 95% confidence interval were calculated. All pooled values to be used for economic modelling (Table 3.7) are given to two decimal places to preserve precision. In all, nine outcome estimates were calculated with 95% confidence intervals for prevalence, sensitivity and specificity (Table 3.7). Six further estimates are given using single study data.

Correlation values were pooled for nine studies (Table 3.8). Most papers had reported Spearman's rank correlation (rho), but Yamada, et al., 2014 used Pearson's correlation coefficient (r). In order to provide a pooled correlation for the Spearman's rho, the large sample approximation for the variance of rho was calculated as 1/(N-1); where N is the total number of subjects from whom the correlation was calculated. Since it is not possible to pool values of rho and r, Yamada's value was considered for meta-analysis as a Spearman's rho coefficient. Sensitivity analysis without Yamada's study made virtually no difference to pooled estimates and so the pooled values including Yamada are reported. 95% confident intervals are only provided where the number of values to be combined is sufficient to give a stable estimate.

Table 3.5: Summary of studies for meta-analysis

References	Study Population	F=0	F=1	F=2	F=3	F=4	Total population
Sporea et al. (2012a)[26]	C	61	241	202	187	223	914
Friedrich-Rust et al. (2013)[25]	B	29	41	13	6	3	92
Friedrich-Rust et al. (2014)[2]	C						Not available
Yamada et al. (2014)[xi]	C	0	84	14	14	12	124
Nishikawa et al. (2014)	C	14	17	32	31	14	108
Chen et al. (2012)	C	0	46	40	23	18	127
Rizzo et al. (2011)	C	13	39	33	24	30	139
Kuroda et al. (2010)	C						Not available
Ye et al. (2012)	B						Not available
Liu et al. (2014)[1]	B	16	26	16	21	29	108

Table 3.6: Summary of outcome data for meta-analysis

References	Study Population	Comparator to Liver Biopsy	Correlation test and r value	Liver Fibrosis per stage	Sensitivity %	Specificity %
Sporea et al (2012) (26)	C	VTq	Spearman r=0.65 (p <0.001)	F≥1	69.9	80
				F≥2	69.1	79.8
				F≥3	74.8	81.5
				F=4	84.3	76.3
Freidrich-Rust et al (2013) (25)	B	VTq	Spearman r=0.42 (p<0.001)	F≥2	50	90
		TE	Spearman r=0.56 (p<0.001)	Not available	Not available	Not available
Friedrich-Rust et al. (2014) (2)	C	VTq	Not available	Not available	Not available	Not available
Yamada et al. (2014)	C	VTq	Pearson r=0.76 (p<0.001)	F≥2	92.5	76.2
				F≥3	84.6	87.8
Nishikawa et al. (2014)	C	VTq	Spearman r=0.73 (p<0.001)	F≥1	69.1	85.7
				F≥2	81.8	87.1
				F≥3	88.9	82.5
				F=4	85.7	86.2
Chen et al. (2012)	C	VTq	Spearman r=0.70 (p<0.001)	F≥2	74.1	87
				F≥3	90.2	89.5
				F=4	88.9	79.8
Rizzo et al. (2011)	C	VTq	Not available	F≥2	81	70
				F≥3	91	86
				F=4	83	86
		TE	Not available	F≥2	71	71
				F≥3	77	85
				F=4	70	82
Kuroda et al. (2010)	C	VTq	Spearman r=0.98 (p=0.002)	Not available	Not available	Not available
Ye et al. (2012)	B	VTq	Spearman r=0.87 (p<0.001)	Not available	Not available	Not available
Liu et al. (2014)	B	VTq	Spearman r=0.85 (p<0.001)	F≥2	83.95	83.05
				F=4	93.1	76.83
		TE	Spearman r=0.81 (p<0.001)	F≥2	81.8	71.24
				F=4	88.1	86.67

Table 3.7: Pooled estimates with 95% confidence interval for prevalence, sensitivity and specificity

Study Population	Comparator to Liver Biopsy	Liver Fibrosis per stage	No. of studies	Prevalence	Sensitivity% (95% CI)	Specificity% (95% CI)
B	VTq	F≥2	2	0.43 (0.06-0.79)	70.02 (31.59-92.19)	87.01 (78.69-92.40)
		F=4	1	0.27 (0.19-0.36)	93.1 (77.23-99.15)	76.83 (66.40-85.90)
	TE	F≥2	1	0.61 (0.51-0.70)	81.8 (70.39-90.24)	71.24 (55.42-84.28)
		F=4	1	0.27 (0.19-0.36)	88.1 (72.65-97.81)	86.67 (77.95-93.76)
C	VTq	F≥1	2	0.91 (0.83-0.95)	69.82 (66.82-72.66)	80.95 (70.44-88.34)
		F≥2	5	0.60 (0.48-0.71)	78.47 (70.04-85.03)	78.96 (73.49-83.55)
		F≥3	5	0.40 (0.32-0.484	85.76 (75.94-91.99)	84.36 (80.69-87.45)
		F=4	4	0.23 (0.18-0.29)	84.48 (79.78-88.24)	81.45 (75.43-86.27)
	TE	F≥2	1	0.63 (0.54-0.71)	71.0 (60.57-80.46)	71.0 (56.92-82.87)
		F≥3	1	0.39 (0.31-0.47)	77.0 (64.40-80.46)	85.0 (75.27-91.60)
		F=4	1	0.22 (0.15-0.29)	70.0 (50.60-85.27)	82.0 (73.09-88.42)
B and C	VTq	F≥2	7	0.55 (0.42-0.67)	77.01 (68.88-83.52)	81.07 (75.83-85.39)
		F=4	5	0.23 (0.18-0.29)	85.03 (80.59-88.60)	80.44 (75.57-84.54)
	TE	F≥2	2	0.62 (0.53-0.70)	76.16 (63.89-85.22)	71.11 (61.17-79.36)
		F=4	2	0.23 (00.14-0.36)	79.43 (55.69-92.22)	83.82 (77.81-88.45)

*Each subgroup classified as separate study

The meta-analysis provided estimates with 95% CIs for prevalence, sensitivity and specificity (Table 3.7). In all, nine pooled outcome estimates were calculated with 95% confidence intervals. Prevalence of significant fibrosis (F≥2) for both hepatitis B and C was lower with VTq (0.55) than TE (0.62), however, the techniques had similar scores for cirrhosis (F=4): VTq: 0.23 and TE: 0.23 respectively.

The results for specificity by all subgroups ranged from 71% to 87%, while for sensitivity the values ranged slightly more widely, from 70% to 93%. The range of values for both sensitivity and specificity were similar for both study populations of hepatitis B and hepatitis C. When comparing significant fibrosis (F≥2) for both hepatitis B and C, VTq had slightly higher values for both sensitivity and specificity (77% and 81%) than for TE (76% and 71%). Values of sensitivity were higher than specificity for cirrhosis (F=4) in the combined study population for VTq (85% and 80%), whilst the opposite was found for TE (79% and 84%). However, the values were similar for both VTq and TE.

Table 3.8: Pooled estimates correlation

Study Population	Comparator to Liver Biopsy	Number of studies	Pooled correlation*
B	VTq	2	0.63
	TE	2	0.69
C	VTq	4	0.68
	TE	Not available	Not available
B and C	VTq	7	0.68 (0.58-0.78)
	TE	2	0.69

*95% confidence interval is only provided where the numbers of studies allow a stable estimate

The meta-analysis of correlation coefficients for VTq and TE gave pooled estimates ranging from 0.63 to 0.69 (Table 3.8). The combined study population correlation coefficients for VTq and TE were similar (0.68 and 0.69 respectively).

3.10 Conclusions on the clinical evidence

The EAC considers that the systematic review was comprehensive; however many of the studies included by the sponsor had overlapping cohorts. These should have been excluded from the review. From the initial 11 studies that the sponsor included, the EAC agrees with the inclusion of 3 studies; 2 with a population of people with hepatitis C, and 1 with a population of people with hepatitis B. All studies included the expected intervention and one or both of the comparators listed in the scope. Many studies were excluded as the population included was mixed or included groups which were not specified in the scope. This reduced the available evidence submitted by the sponsor substantially.

The evidence provided did not cover all of the outcomes listed in the scope, but the EAC agrees with the sponsor that several of the listed outcomes were secondary outcomes. These secondary outcomes have not been investigated specifically in any of the clinical studies.

The EAC considered that the sponsor's interpretation of the available evidence was reasonable, and provided a fair assessment of the strengths and weaknesses.

As the sponsor had not performed their own meta-analysis, and to ensure that all available evidence had been identified, the EAC repeated the systematic review and performed a meta-analysis. The EAC's systematic review identified 10 studies, which included the 3 identified by the sponsor, 2 that had been previously excluded by the sponsor, and 5 additional studies.

The meta-analysis of the comparators (VTq and TE) to liver biopsy was carried out by the EAC to fill the gaps in the evidence base by providing additional pooled outcome estimates with 95% confidence intervals. The pooled estimates of prevalence, sensitivity and specificity were the parameters required for the economic modelling and pooled estimates for correlation were also provided. The meta-analysis provided pooled estimates

for the various study populations (hepatitis B, hepatitis C or combined study populations) and for liver fibrosis stage. Not all liver fibrosis stages were able to be included in the meta-analysis, however, pooled estimates were available for all F≥2 and F=4 subgroups.

As expected, prevalence rates generally decreased with increasing liver fibrosis stage. Overall prevalence for both VTq and TE (combined study populations) had similar rates for cirrhosis (F=4) (0.23 vs. 0.23), and a lower prevalence for significant fibrosis (F≥2) for VTq when compared to TE (0.55 vs. 0.62). Pooled estimates (combined study populations) for correlation were similar for VTq and TE, whilst the pooled estimates for sensitivity for significant fibrosis (F≥2) and cirrhosis (F=4) were higher for VTq in comparison to TE. Specificity values for significant fibrosis (F≥2) were notably higher for VTq than TE (81% vs. 71%), but were closer for cirrhosis (F=4) (80 vs. 84%).

The EAC notes that caution must be observed when interpreting the results from the meta-analysis as no adjustment is made for confounding variables such as patient characteristics (other than hepatitis type), research design and research settings (such as country). This is due to the lack of detailed information available in the studies accepted and included in the meta-analysis by the EAC. This limitation is discussed further in section 7.

4 Economic evidence

4.2 Published economic evidence

Critique of the sponsor's search strategy

The sponsor submitted a search strategy designed to retrieve relevant health economics studies from published and unpublished literature. The following databases were searched: Medline (PubMed), EMBASE, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database. The search combined terms related to the target condition (hepatitis), the intervention (VTq, referred to by the sponsor as ARFI), and/or the comparator (TE, referred to as Fibroscan) and economics. Health technology assessments which looked at the cost of TE and/or liver biopsy in the assessment of fibrosis from any aetiology were also viewed as suitable source material. The date span of the search was from 2009 to 2014, since the sponsor determined that the first papers on VTq were published in 2009.

In total, 61 publications (title and abstracts) were reviewed for further full text retrieval and assessment. Based on defined inclusion and exclusion criteria, 9 papers plus one Centre for Evidence-based Purchasing economic report on ultrasound elastography were retrieved for full text assessment. The sponsor selected five studies (Stamuli, Kruger and Hutton, 2009, Stevenson, et al., 2012, Canavan, et al., 2013, Steadman, et al., 2013, Whitty, et al., 2014) related to comparators for final review.

The EAC reviewed the sponsor's search strategy and databases included and concluded that it could be improved in three ways. Firstly, the date span of the search could be extended to confirm that no older publications were missed, and to substantiate the sponsor's claim that the first papers on VTq were published in 2009. Secondly, the search terms could be more comprehensive. More specifically, search terms on the technology 'virtual touch tissue quantification' could have been included. Finally, whilst the sponsor has included the HTA databases, the EAC considered that the NHS Economic

Evaluation Database (NHS EED) and Econlit databases should also have been included.

Given these issues, the EAC undertook a new search for economic evidence related to the technology and comparators. The databases included were Medline & Medline(R) In-Process & Other Non-Indexed Citations, Embase, ECONLIT, NHS EED and HTA databases and the search covered the time period 2000 to 2014. The detailed search strategies are included in Appendix 6.

Critique of the sponsor's study selection

The sponsor selected studies using the following inclusion criteria based on the scope: population (liver fibrosis), interventions (ARFI using VTq and/or liver biopsy and/or TE), outcomes (cost of intervention), study design (economic analysis), language restrictions (English abstracts), and search dates (2009 to 2014). The exclusion criteria used were: population (undefined liver disease), interventions (other tests), 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) and language restrictions (English abstract unavailable). The EAC reviewed the inclusion and exclusion criteria and determined that they were appropriate, except for the date of the search which could have been extended. The EAC used 2000 to 2014 as the span of search in its revised search strategy.

Included and excluded studies

Using appropriate inclusion and exclusion criteria, the sponsor found no published evidence related to the technology from the search. The sponsor found five studies (Stamuli, Kruger and Hutton, 2009, Stevenson, et al., 2012, Canavan, et al., 2013, Steadman, et al., 2013, Whitty, et al., 2014) related to the comparators (TE and liver biopsy) after final review. Quality assessments were also provided for these studies. Although the EAC considers that the included studies related to the comparators are not directly relevant to this

evaluation, they could nevertheless be used as a good source of evidence for modelling purposes.

The EAC in its search found no economic evidence related to the technology, confirming the conclusion by the sponsor that there is no published evidence related to the technology. The EAC found papers related to the comparators (TE and liver biopsy) only. The sponsor's inclusion of papers related to the comparators covered most of the published evidence. The EAC found one additional paper (Carlson, et al., 2009) related to the comparators, which could be added to the sources of evidence for modelling purposes.

Overview of methodologies of all included economic studies

Not applicable as the sponsor has not included any economic studies related to the technology.

Overview and critique of the sponsor's critical appraisal for each study

Not applicable as the sponsor has not included any economic studies related to the technology.

Does the sponsor's review of economic evidence draw conclusions from the data available?

Not applicable as the sponsor has not included any economic studies related to the technology. The EAC also did not find any evidence on the technology, substantiating the conclusions reached by the sponsor that no economic evidence is available for the technology.

4.3 De novo cost analysis

Since no economic evidence was available for the VTq technology, the sponsor submitted a cost model. This is a short-term cost model evaluating: 1) the technology, i.e. VTq and, if needed, liver biopsy, against two comparator strategies: 2) TE and, if needed, liver biopsy; and 3) liver biopsy only.

The EAC considers that the proposed model generally addresses the scope issued by NICE, but nonetheless, has important issues that need to be addressed. Particularly, the model structure proposed by the sponsor neither: 1) reflects the clinical pathways for patients with fibrosis (both the current pathways with TE and liver biopsy and the proposed pathway with VTq); nor 2) takes into account all relevant costs and outcomes for diagnosing and treating liver fibrosis. On this basis, the EAC considered it necessary to remodel the sponsor's approach before any conclusion could be drawn. The following sections provide some insight into the key issues to be addressed.

Patients

The patient group used in the cost analysis included patients suffering from chronic hepatitis B or hepatitis C in whom assessment of liver fibrosis was indicated. This was aligned with the population defined in the scope.

Technology

The technology included by the sponsor for the cost analysis was VTq.

Comparator(s)

The comparators considered were TE and liver biopsy. Two strategies have been considered as comparators: 1) a combined strategy, i.e. TE and – if needed –liver biopsy; and 2) a stand-alone strategy, i.e. liver biopsy only.

Model structure

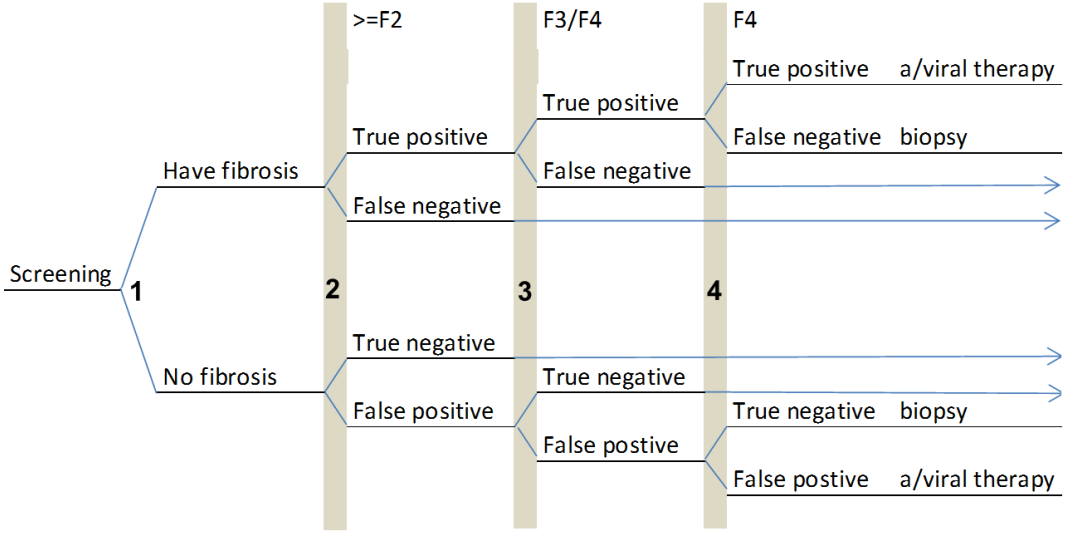
The sponsor provided a decision tree model using 2013 prices from the NHS and personal social services perspective to estimate the cost for VTq and the comparators. Although not clear in the model (see figure 4.1) the EAC believes that VTq was assumed to be a direct replacement of TE in the

combined strategy whilst liver biopsy was regarded as the reference test for liver fibrosis (i.e. it has 100% accuracy). The EAC agreed with this assumption.

The sponsor's modelling approach seems to be based on a 2009 economic report from the Centre for Evidence-based Purchasing (Stamuli, Kruger and Hutton, 2009). However, this report does not seem to include the distribution of different stages of liver fibrosis stage (i.e. F1 to F4 using Metavir Score) (Stamuli, Kruger and Hutton, 2009). Therefore, the model proposed by Stamuli et al. (2009) would not be appropriate to fully capture the decision problem stated in the scope issued by NICE. In order to mitigate this issue, the sponsor has proposed a revised model using a sequential distribution of liver fibrosis stage (according to Metavir score). This is achieved by sequentially separating the overall prevalence of liver fibrosis in three stage groups: i) equal or greater than F2 (≥F2); ii) F3 or F4; and iii) F4. The modelling was developed using two parameters: 1) estimated prevalence of liver fibrosis for different stages; and 2) the sensitivity/specificity of each strategy (i.e. VTq and the comparators - TE and liver biopsy) at different liver fibrosis stages. Based on the above mentioned parameters, all patients were categorised as: i) true positive; ii) true negative; iii) false positive; or iv) false negative (see figure 4.1).

As illustrated in figure 4.1, no treatment or ongoing monitoring has been allowed for in patients with ≥F2 and F3/F4 liver fibrosis stage (i.e. upper branches containing the true positive and false negative arms in chance nodes 2 and 3, as highlighted in figure 4.1). In chance node 4, i.e. F4 liver fibrosis patients, all true positive patients received antiviral treatment whilst false negative patients received a biopsy. Similarly all true negative patients have been considered to receive a biopsy. The EAC does not understand this rationale and furthermore did not find any evidence that this assumption was indeed included in the economic model. Finally, all false positive F4 patients have also received antiviral treatment, consistent with clinical practice.

Figure 4.1: Model structure



The EAC agrees with this rationale. However the EAC also considers that the model proposed by the sponsor fails to address relevant costs and outcomes, such as:

- Ongoing costs of fibrosis monitoring and treatment as stated in the scope issued by NICE. The sponsor's model has failed to recognise all relevant costs incurred by the health system in the monitoring and particularly the treatment of liver fibrosis. In fact, apart from patients with severe liver fibrosis (Metavir score F4), no monitoring or treatment costs were included. Therefore, the model implicitly considered that there was no added value in the diagnosis (and potential treatment) of stage F1-F3 liver fibrosis. The EAC disagrees with this approach, which does not reflect current clinical practice. The opposite is true, particularly for patients with F3 liver fibrosis as they might benefit from treatment strategies.

- No additional costs were considered for patients misclassified as negative patients (i.e. false negatives or patients with liver fibrosis misclassified as patients without liver fibrosis). The sponsor has stated that misclassified patients will re-enter the model as 'new' patients. The EAC considered that this assumption is not appropriate and is potentially misleading, particularly for false negative patients with F3

and F4 liver fibrosis. In fact, disease misdiagnosis holds a real cost (e.g. need to repeat exams, inpatient treatment, A&E attendance related to ongoing symptoms).

- Although specified in the economic submission, no mortality associated with liver biopsy seemed to be modelled. The sponsor presented an additional £7 unit cost for liver biopsy due to treatment costs associated with major adverse event (death) but no 'mortality arm' was included in the model. As the 2014 PbR tariff was used to cost a liver biopsy, the extra £7 unit cost was assumed to have been included in the PBR tariff. Although no probability of death was included, the EAC believes that this issue is unlikely to have any impact on the evaluation since this major adverse event is very uncommon (1/10,000) in a liver biopsy test. However for completeness, the EAC recommends including mortality in the model.

As a consequence of these concerns, the EAC considered it necessary to revise the model proposed by the sponsor (see section 4.5 for further details). The revised model should include: 1) a revised overall model structure that better depicts clinical practice; 2) an additional cost for diagnosis and treatment of F3-F4 liver fibrosis patients initially misclassified as negative (i.e. false negative); 3) a cost for ongoing monitoring of all F1-F2 liver fibrosis patients; and 4) a new branch including mortality associated with liver biopsy.

The cost analysis presented by the sponsor is based on a 1,000 patient cohort. This is not aligned with NICE's cost-consequence methodology which relies on a cost per patient approach.

Clinical parameters and variables

No specific time horizon for the cost model has been presented by the sponsor. In line with the sponsor's submission, the EAC believes that most of

the costs and outcomes are likely to be realised in the short-term. In some cases, such as for F4 positive patients, antiviral therapy can last up to 48 weeks. With this in mind, the EAC considered that the short-term decision tree model should present a one-year time horizon.

The sponsor's model was based on two key clinical variables: 1) overall prevalence of liver fibrosis and its distribution for different stages; and 2) accuracy levels of VTq and TE to diagnose liver fibrosis. These two variables determine the positive predictive value (PPV) and negative predictive value (NPV) of each diagnostic tool. The sponsor's model then takes a sequential approach (i.e. starts with the initial overall prevalence of liver fibrosis which is then subsequently divided between different stages of severity). Positive and negative findings are divided using sensitivity and specificity. The EAC generally agreed with this approach.

The overall prevalence of liver fibrosis and, quite importantly, its distribution across liver fibrosis stages seems to be difficult to estimate. The sponsor presented some clinical estimates based on expert advice. One expert adviser estimated the overall prevalence of liver fibrosis equal to or higher than F2 to be around 15% (the EAC deduces that the sponsor and the clinical expert were referring to 15% of the total cohort of patients with chronic hepatitis B and C in whom liver fibrosis was indicated). The sponsor also provided a literature reference for a F4 liver fibrosis prevalence of 35% (Stevenson, et al., 2012). However, this reference refers to a study based on a population with liver fibrosis with suspected alcohol-related disease and therefore not aligned with the scope. To minimise these shortcomings, the EAC contacted NICE's clinical experts. Three expert advisers said that they did not know the prevalence rates and one expert adviser (a hepatologist) expressed the opinion that it is difficult to find any reliable UK data.

Sensitivity and specificity values for TE were retrieved by the sponsor from a meta-analysis by Steadman et al. (2013). The median value is assumed as the base case in the diagnosis of three groups of patients: i) ≥ F2; ii) F3 or F4;

and iii) F4. The 25th and 75th percentile values were used for the best and worst case scenarios respectively for sensitivity analysis.

VTq's sensitivity and specificity for different stages of liver fibrosis were estimated from different published studies, i.e. not from a meta-analysis. Essentially, the sponsor seems to have listed the different sensitivity and specificity values for different fibrosis stages and to have estimated the median and 25th and 75th percentile. The EAC considered this methodology as lacking the necessary robustness for the purpose of the present cost analysis. For this reason, the EAC performed a meta-analysis focussing on VTq and TE sensitivity and specificity for different liver fibrosis stages.

Liver biopsy was assumed to have perfect (i.e. 100%) sensitivity and specificity, as it is the reference test for diagnosing liver fibrosis. The EAC agreed with this assumption.

Resource identification, measurement and valuation

All direct costs related to performing a VTq assessment, a TE exam or a liver biopsy were considered by the sponsor in the next section 'Technology and comparators' costs'.

The result of initial assessment with VTq or TE or liver biopsy can be that the patients either: 1) have liver fibrosis (positive patients); or 2) do not have liver fibrosis (negative patients).

In the first group, i.e. the positive patients, a proportion of patients are true positive and the remaining false positive (note: this is not applicable to liver biopsy which was assumed to have 100% sensitivity and specificity). The sponsor assumed that all patients with F4 liver fibrosis (using Metavir score) will receive antiviral therapy. This is aligned with the proposed clinical pathway. This means that both false and true positive patients will receive treatment. The EAC does not understand the sponsor's underlying basis for the proposed base case of £10,000 for the treatment of F4 positive patients

(present in the Microsoft Excel file containing the economic model proposed by the sponsor). On the other hand, all non-F4 liver fibrosis patients (i.e. patients with F1 to F3 liver fibrosis) were not considered to have additional monitoring or treatment. The EAC believes that this does not reflect clinical practice as these patients, particularly the F3 liver fibrosis patients, are likely to receive treatment. The F1 and F2 liver fibrosis patients are likely to enter a 'watchful waiting' strategy with regular monitoring of the disease progression.

In the second group, i.e. negative patients, no treatment or monitoring costs were considered. This was appropriate for the true negative patients but inappropriate for the false negatives who may go on to incur costs associated with their symptoms. The EAC disagrees with the sponsor's assumption that these patients will re-enter the model as 'new' patients. Due to such issues, the EAC considers it relevant to add monitoring and treatment costs to the model, particularly for misdiagnosed patients with more severe liver fibrosis (F3 and F4 according to Metavir score).

Technology and comparators costs

The sponsor has undertaken and presented a bottom-up approach for costing the technology (VTq; £15.02 per scan) and one of the comparators (TE; £25.33 per scan), as there are no specific tariffs that accurately reflect differences in resource use. The EAC agrees with this for the reasons detailed below.

With regards to TE, the sponsor has presented two options that the EAC considers appropriate: 1) a bottom-up costing approach presented in the 2009 CEP report (Stamuli, Kruger and Hutton, 2009), suggesting a £18.68 (corrected for inflation £22.91 in 2014) TE unit cost; and 2) a revised bottom-up approach presented by the sponsor, with a unit cost of £25.33. There was a marginal difference between the two estimates (around 10%), mainly due to variation in the annual patient throughput considered (5,000 patients in the CEP report and 2,500 in the sponsor submission). Taking into consideration

such minimal variation, the EAC accepts the TE unit cost proposed by the sponsor and submitted this parameter to sensitivity analyses in the revised model developed by the EAC.

The unit cost per VTq exam has been estimated by a bottom-up approach. The sponsor has presented a unit cost based on: 1) capital costs (Acuson S2000 US System £59,700 and VTq Software £4,415 excluding VAT); 2) annual maintenance costs (yr 2 of £2,246); 3) staffing costs (exam to be performed by a Band 7 Radiographer); and 4) departmental overheads assuming a 4 square meter space to use the Acuson S2000 US System. The EAC agrees with the sponsor's rationale but pursued a different approach to double check staffing costs. Assuming: 1) a 10 minute appointment length to perform a VTq scan; and 2) that the scan is performed by a hospital radiographer at a rate of £37 per hour (Curtis, 2013), the EAC estimated a £6.17 staffing cost per patient, and an overall cost consistent with the cost presented by the sponsor (£15.02). However, to estimate annual capital costs for VTq and TE, the sponsor divided the total capital cost by equipment lifetime. This approach has limitation in economic costing, since opportunity cost is not taken into account. The standard method to estimate annual cost is to use the 'annuity method' as described in standard textbooks (Drummond, et al., 2005). The test cost thus required re-estimation using the annuity method. Similarly to testing of the TE unit cost, the VTq unit cost was submitted to sensitivity analyses in the revised model developed by the EAC.

The biopsy unit cost (£615 per liver biopsy) was estimated from the 2013-14 payment by results (PbR) tariff, assuming a mix of different procedures with varying tariffs (£535 or £973 according to the sponsor). Potential costs associated with liver biopsy complications are assumed to be included in the tariffs mentioned. The EAC agrees that it is reasonable to use reimbursement tariffs to estimate the unit cost per liver biopsy, but recommends using the appropriate NHS reference codes (Department of Health, 2013) to estimate the cost of liver biopsy. The sponsor failed to explain the exact mix of

procedures assumed in order to estimate an overall £615 unit cost per liver biopsy.

Sensitivity analysis

The sponsor performed several deterministic one-way and multi-way sensitivity analyses, varying: 1) the prevalence of liver fibrosis; 2) VTq's diagnostic accuracy; 3) specific costs (e.g. unit cost per VTq exam); and 4) biopsy utilisation after initial diagnostic ultrasound. In the sensitivity analysis the best, worst and likely (i.e. base-case scenario) were considered. The EAC considered this approach reasonable. Nevertheless, the EAC found it particularly hard to understand the different prevalence estimates for different liver fibrosis stages and other approaches used by the sponsor (i.e. difficult to match the Microsoft Excel file containing the economic model with the economic submission). Below, and in section 4.3 of the present document, the EAC addressed the issues found in the sensitivity analysis sections (i.e. sections 9.4. and 9.5.6. to 9.5.9. of the sponsor's submission). The revised model developed by the EAC also included other variables in the sensitivity analyses (see section 4.5 for further detail).

No specific consideration was given to the scenarios with and without a compatible Siemens ultrasound machine as requested in the scope. This means that the impact of ownership of an existing Acuson S2000 or Acuson S3000 system was not estimated. The EAC believes that this could have an impact on cost-savings per patient. The EAC modelled this scenario by revising the unit cost per VTq exam to include and exclude the Acuson machine cost.

In summary, the EAC believes that the sponsor has included most of the relevant parameters, although no proper rationale for all the sensitivity analyses intervals has been provided (e.g. variation of prevalence per liver fibrosis stage, considering 20% of patients receive biopsy – compared to the 100% base-case scenario).

4.4 Results of de novo cost analysis

Base-case analysis results

The sponsor has claimed that the results are expressed as cost per patient. The EAC disagrees given that – as highlighted in section 4.2 under the heading 'Resource identification, measurement and valuation' – not all relevant costs have been considered.

The sponsor has reported a cost saving per patient of £10.31 for VTq compared to TE (see Table C12 in page 122). On the other hand, in comparison with the biopsy the sponsor has reported that the utilisation of VTq might lead to a cost-savings of around £599.08 per patient (see Table C12 in page 122).

Sensitivity analysis results

Overall prevalence of liver fibrosis has been varied from the 15% in the base-case scenario to a range 15%-45% in the one-way deterministic sensitivity analysis (according to Table C10.1 in page 118 of the economic submission). The EAC did not find the results derived from the one-way sensitivity analysis in the sponsor's submission. In fact, the results presented under section 9.5.6 (page 124 of the submission) seem to relate to the multi-way sensitivity analyses (as per Table C10.2 1 in page 118) and not the intended one-way sensitivity analysis (as per Table C10.1 in page 118). In summary, the EAC believes that: 1) the one-way sensitivity analysis results are not presented in the report; and 2) the results from the multi-way sensitivity analysis are presented under section 9.5.6 (page 124) and not section 9.5.7 (page 128) as intended.

A further multi-way sensitivity analysis was also performed using liver disease prevalence of 10%-30%, as well as varying prevalence for different liver fibrosis stages. The EAC believes that this variation in overall prevalence

(presented in Table C10.2 on page 118) and in the prevalence of different fibrosis stages (no values have been presented by the sponsor in the economic submission) lacks a robust rationale). Increasing overall prevalence of liver fibrosis from 10% to 30% generated a moderate 15% reduction in the cost-savings per patient, decreasing from £527 to £447.

VTq's sensitivity and specificity were also varied for each liver fibrosis stage group according to the 25th and 75th percentile gathered from literature review. However, as stated above, these figures – as opposed to the ones related to one of the comparators (TE) - were not retrieved using a robust methodological approach, i.e. a meta-analysis. Varying the sensitivity and specificity from the best-case scenario (i.e. 25th percentile) to the worst-case scenario (i.e. 75th percentile) at liver fibrosis prevalence level of 15% (see Table C15b in page 126) produces a modest 6% reduction in the cost per patient, decreasing from £507 to £476 (as highlighted in Table C16a in page 128).

The sponsor has also included in the multi-way sensitivity analysis a variation of the biopsy utilisation rate in the comparison biopsy-only strategy, decreasing it from the 100% base-case scenario to just 20%. The EAC did not find this variable in Table C10.2 (on page 118) and could not understand the rationale behind the 20% assumption. This parameter has a huge impact on the cost-saving, decreasing it from £527 to just over £15 (assuming a 15% overall prevalence) (see Table C16b in page 129). In addition, combined with other variations (e.g. decrease in VTq accuracy levels or increase in liver fibrosis prevalence) the VTq strategy might be even be more expensive.

Although the sponsor has stated that it is included in the economic submission, the EAC found little evidence regarding sensitivity analysis around cost parameters, particularly the unit cost of VTq (as no results from the one-way sensitivity analysis were found in section 9.5.6., page 124). Actually, cost-wise the only variation found was in the multi-way sensitivity analyses presented in Table C16c (page 130) where the sponsor has explored a decrease in the liver biopsy utilisation rate combined with a

decrease in the cost of antiviral treatment (i.e. treatment of F4 false positive and true positive patients). As mentioned earlier, the results illustrated in Table C16b and C16c both lack evidence as no rationale was presented by the sponsor (i.e. there is no mention of these analyses in section 9.4.2 and Table C10.2 on page 118).

The EAC advises caution in the interpretation of the results as missing costs and outcomes in the sponsor's model might also change the findings presented (see section 4.5 of this document for further detail).

Subgroup analysis

No subgroup analysis was required or performed.

Model validation

The sponsor's model has been based on (Stamuli, Kruger and Hutton, 2009) and revised to address the final scope issued by NICE. The EAC believes the model presents internal validity. In fact, the electronic version of the model proposed (the Microsoft Excel file) seems to be accurately defined despite some variables - particularly in the multi-way sensitivity analysis - lacking proper rationale/justification in the economic submission.

The sponsor has acknowledged that the TE and VTq accuracy levels are equivalent and therefore any variation in the cost-consequence will result from the difference in the unit cost of the techniques. The EAC understands this rationale, but opted to revise the sponsor's model to clearly accommodate the issues identified.

4.5 Interpretation of economic evidence

The sponsor has not included any economic studies related to the technology, and the EAC confirmed that no economic evidence is available. Economic evidence is available only for the comparators (TE and liver biopsy), but in the

view of the EAC, these pieces of evidence are not relevant to this assessment. Since economic evidence for the technology is not available, the sponsor has submitted a de novo cost model. The sponsor's cost model shows a cost-savings per patient of £10.31 by using VTq compared to TE, and in comparison with liver biopsy the sponsor has shown a cost-saving of around £599.08 per patient. The EAC believes that the submitted model has not taken account of all relevant costs and outcomes for diagnosing and treating liver fibrosis. On this basis, the EAC considers it necessary to remodel the sponsor's approach before any conclusion can be drawn.

4.6 Additional work undertaken by the External Assessment Centre in relation to economic evidence

Given the issues related to the model submitted by the sponsor, the EAC remodelled the cost of VTq as compared to TE and liver biopsy. A short-term decision model based on the results of the meta-analysis performed by the EAC was constructed. One of the limitations of the meta-analysis was that prevalence, sensitivity and specificity were available only for patients with liver fibrosis; i) F≥2 and F=4 for combined Hepatitis B and Hepatitis C; and ii) for F≥3 only in the Hepatitis C population. Ideally, the cost model should have been modelled using prevalence, sensitivity and specificity for the different fibrosis stages separately. This would have helped develop a much more robust model.

Due to data limitations, the EAC also developed a sequential model, with a similar rationale to that proposed by the sponsor. In the model constructed by the EAC, the misdiagnoses (i.e. false negatives and false positives) were also included as arms in the decision model. The prevalence, sensitivity and specificity used in the revised model were based on the meta-analysis performed by the EAC.

The expected cost per patient is presented in the results. The NICE scope requested scenarios considered in the model to include settings where there is a compatible Siemens ultrasound machine and those without. The base case model includes the capital costs related to purchasing a new compatible

Siemens ultrasound machine. Results of a scenario where a compatible Siemens ultrasound machine (with cost for Acuson machine excluded) is already available are also presented.

Model Structure

The revised model sequentially modelled F≥2, F≥3 and F=4 for VTq, TE and liver biopsy use in adults or children with chronic hepatitis B or C in whom assessment of liver fibrosis is indicated. Prevalence, sensitivity and specificity for each stage in the sequence, calculated separately for VTq, TE and liver biopsy, were used to develop the model structure. At each stage in the sequence true positives, false negatives, true negatives and false positives were included. The model structure is built on several important assumptions:

1) Patients with liver fibrosis and negative results (i.e. false negative) are likely to return for diagnosis within a year (as clinical symptoms will persist) and will be diagnosed as true positives with an additional test. Therefore, with reference to the model, patients with initial (false) negative findings were subsequently modelled as (true) positive for liver fibrosis;

2) False positives might be assigned to different fibrosis stages and were included as misclassified fibrosis in the revised model;

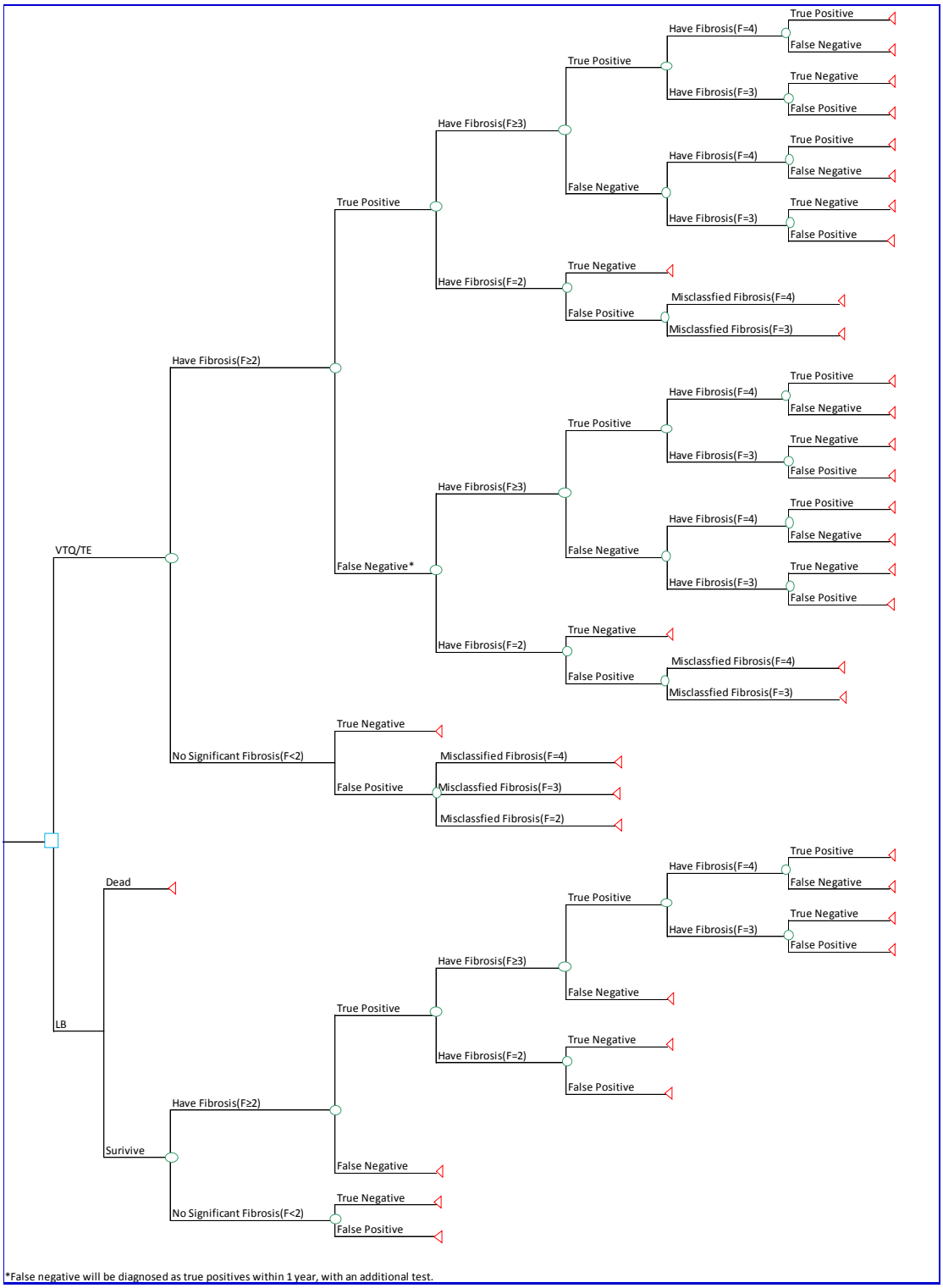
3) Liver biopsy is considered to have perfect sensitivity and specificity values (100 %) as it is the gold standard reference against which the non-invasive testing strategies were developed;

4) Liver fibrosis disease progression was reported in literature to be slow (Carlson, et al., 2009). Furthermore, a NICE appointed hepatologist expert adviser also stated that for HCV, the progression from F0 at infection to F4 cirrhosis takes 20-30 years, but not all progress at this rate. For HBV, variability was greater depending upon host factors, progression through virological life cycles, age at infection etc. As such, the time to progression can be between 5 years and 50 years or more. This implied to the EAC that; 1) no clinical impact results from the potential treatment delay due to an initial

misdiagnosis (only applies to the VTq and TE models); and 2) long-term modelling of disease progression in this evaluation was not required.

The model structure for VTq, TE and liver biopsy is presented in figure 4.2. The time horizon for the model was 1 year. The EAC considers this time horizon as sufficiently long to reflect any differences in costs and consequences between the technologies being compared.

Figure 4.2 – Model Structure



Assumptions

The assumptions on probabilities and costings used in the models are presented in Table 4.1.

Probabilities for liver fibrosis prevalence and VTq and TE sensitivity and specificity for different liver fibrosis stages (Metavir score F≥2, F≥3 and F=4) were taken from the EAC's meta-analysis (Table 3.7). Key considerations with regard to these key parameters are as follows:

- Prevalence for different stages of fibrosis obtained from the meta-analysis was different for VTq and TE. This might be due to patient selection in the included studies. In order to make the cost modelling comparable between VTq, TE and liver biopsy, the combined hepatitis B and hepatitis C prevalence rates for different liver fibrosis stages in the VTq model were also used for TE and liver biopsy models;

- Prevalence rates, sensitivity and specificity in the combined groups (i.e. hepatitis B and hepatitis C) were available only for specific liver fibrosis stages (Metavir score F≥2 and F=4). However, prevalence rate, sensitivity and specificity for F≥3 were available for hepatitis C. This was assumed to be applicable to both groups and was used in the model. This probability was subjected to sensitivity analysis due to its uncertainty;

- Sensitivity and specificity for liver biopsy were assumed to be 100%, since liver biopsy is the gold standard reference test;

- The model assumed that patients with liver fibrosis score F≥2 have fibrosis and that those with lower scores have no significant fibrosis;

- In the sequential model, all false negatives for F≥2 were assumed to re-present within 1 year due to persisting symptoms and were assumed to be detected as true positives with an additional test.

Hence, false negatives for F≥2 were given two tests and were modelled as true positives. This means that monitoring and treatment costs – particularly for patients with liver fibrosis F3 and F4 - were considered, even if the initial test exhibited (false) negative findings;

- Some patients without significant liver fibrosis (i.e. 'no significant fibrosis (F<2) arm in the VTq/TE model)would have initial positive findings which would misclassify them as either F2, F3 or F4. The distribution of these patients across the stages was unknown. It was therefore necessary to arbitrarily assume that the majority of the misclassified cases would be F2 (i.e. the least severe liver fibrosis stage). This assumption was subjected to sensitivity analysis;

- For those patients identified with significant fibrosis (Metavir score F≥2) who should go on to be classified as F=2, a portion will be misclassified as either F3 or F4. Again, the distribution of the misclassification across F3 and F4 was unknown and therefore had to be chosen arbitrarily. The distribution was subjected to sensitivity analysis; and

- A mortality risk of 0.003 was assumed for liver biopsy, based on literature (Canavan, et al., 2013). No additional cost of mortality was included since it is assumed that it would have been included in the test cost.

Cost estimates were based on the sponsor's submission and literature. The assumptions on costs used in the model are as follows:

- Although the bottom-up approach used by the sponsor to estimate the unit costs of VTq and TE tests was considered reasonable by the EAC, the EAC made minor changes to the estimation. To estimate annual capital costs for VTq and TE, the sponsor divided the capital cost by its life years. This approach has limitation in economic costing, since opportunity cost is not taken into account. The standard method

to estimate annual cost is to use the ‘annuity method’ as described in standard textbooks (Drummond, et al., 2005). A discount rate of 3% was used to estimate the annual cost. This re-estimation marginally changed the test unit cost for VTq (£15.24) and TE (£25.90). These values were considered in the model.

- The liver biopsy unit cost (£615 per liver biopsy exam) was estimated from the 2013-14 payment by results (PbR) tariff by the sponsor. The EAC checked the appropriate tariff in the NHS reference cost (Weighted average of NHS reference tariff codes GB04D (Minor Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, 19 years and over) and GB04E (Minor Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, 18 years and under) and estimated it to be £622 (Department of Health, 2013). This value was incorporated in the model.

- All patients categorised as F3 or F4 (either due to false positive or true positive findings) were assumed to undergo antiviral therapy. Since the EAC did not find any therapy cost evidence available for fibrosis stage F3 and F4, some assumptions were used. The NICE technology appraisal - Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (TA200)’(National Insitute for Health and Clinical Excellence, 2010) reported the costs of antiviral therapy for 12 weeks and 24 weeks. The antiviral therapy required for patients with F3 and F4 liver fibrosis were assumed to be equivalent to 12 and 24 weeks course of treatment, respectively. The NICE guidance reported the therapy cost according to genotypes which was averaged and inflated to 2013 prices. The estimated cost used in the model was £2,808 (patients with F3 liver fibrosis) and £5,680 (patients with F4 liver fibrosis). As there was uncertainty around this cost estimate, a sensitivity analysis was performed.

- The cost for each arm of the decision model was based on costing assumptions presented in Table 4.2.

Sensitivity Analysis

As there was uncertainty surrounding some of the key variables used in the cost model, deterministic sensitivity analysis was performed to check the robustness of cost savings estimated for VTq against TE and liver biopsy. The variables varied in the sensitivity analysis were:

- Prevalence, sensitivity and specificity for VTq and TE were varied to a low and high level. The range used in the sensitivity analysis was based on the confidence intervals reported in the meta-analysis performed by the EAC (Table 3.7);

- The false positive misclassification distribution (Metavir score F=2 and F=3) was varied to a low proportion of 60% and a high proportion of 90%. This range was arbitrarily chosen;

- The unit cost of the VTq test used in the base-case scenario assumes that a compatible Siemens ultrasound machine with the VTq software needs to be purchased. In an alternative scenario, where a compatible Siemens ultrasound machine is already available, the unit cost of the VTq test is £11.98 (with cost for Acuson machine excluded). Sensitivity analysis using £11.98 as a low test cost and a high test cost equal to that of the TE test (£25.90) has been considered;

- The unit cost of the TE test has been estimated by the sponsor assuming that it is used for 5 half-day sessions per week (2,500 patients annually). Due to uncertainty in this estimate, sensitivity analysis using the cost of TE used for 2 sessions (1,000 patients annually) per week (£42.06) and 8 sessions (4,000 patients annually) per week (£16.19) were also considered;

- The antiviral therapy cost for F3 and F4 were subjected to a 20% and 50% variation. This range was arbitrarily chosen.

Table 4.1: Probabilities and costs

	VTq			TE			LB¬		
	F≥2	F≥3*	F=4	F≥2	F≥3*	F=4	F≥2	F≥3*	F=4
Prevalence^	0.55	0.40	0.23	0.55	0.40	0.23	0.55	0.40	0.23
Sequential Prevalence	0.55	0.73	0.57	0.55	0.73	0.57	0.55	0.73	0.57
FP Misclassification Distribution (F≥2)"	0.75	0.15	0.10	0.75	0.15	0.10			
FP Misclassification Distribution (F≥3)"		0.75	0.25		0.75	0.25			
Sensitivity	77.01	85.76	85.03	76.16	77.00	79.43	100	100	100
True Positive(TP)	0.42	0.34	0.20	0.42	0.31	0.18	0.55	0.40	0.23
False Negative(FN)	0.13	0.06	0.03	0.13	0.09	0.05	0.00	0.00	0.00
Arm Probability(TP)	0.77	0.86	0.85	0.76	0.77	0.79	1.00	1.00	1.00
Arm Probability(FN)	0.23	0.14	0.15	0.24	0.23	0.21	0.00	0.00	0.00
Specificity	81.07	84.36	80.44	71.11	85.00	83.82	100	100	100
True Negative(TN)	0.37	0.50	0.62	0.32	0.51	0.65	0.45	0.60	0.77
False Positive(FP)	0.09	0.09	0.15	0.13	0.09	0.12	0.00	0.00	0.00
Arm Probability(TN)	0.81	0.84	0.80	0.71	0.85	0.84	1.00	1.00	1.00
Arm Probability(FP)	0.19	0.16	0.20	0.29	0.15	0.16	0.00	0.00	0.00
Mortality$	-			-			0.003		
Test Cost(£)¬	15.24			25.9			622		
Antiviral treatment Cost(£)	0	2,808	5,680	0	£ 2,808	£ 5,680	0	£2,808	£ 5,680

Antiviral treatment Cost Estimation

	12 Wks	24 Wks	Assumption
HCV Genotype 2 & 3(Course of therapy)[1]	2508	5139	AVT treatment for F3(12 weeks) and F4(24 weeks)
HCV Genotype 1,4,5 & 6 (Course of therapy)[1]	2867	5734	
Average cost(2010)	£ 2,688	£ 5,436	
Average cost (2013)- Inflated with HCHS index	**£ 2,808**	**£ 5,680**	

Assumptions

^ Prevalence used for modelling VTq, TE and LB are from meta-analysis of VTq studies
"Distributions are for individual stages(F2, F3 & F4)
* Assumption based on meta-analysis of VTq(HCV) studies
$ Canavan et al 2013
¬ Source: Vtq and TE test cost(Sponsor's submission). LB test cost(Weighted average of NHS reference tariff codes GB04D(Minor Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, 19 years and over) and GB04E(Minor Endoscopic or Percutaneous, Hepatobiliary or Pancreatic Procedures, 18 years and under))
[1] National Institute for Health and Care Excellence (2010). NICE TA200. Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C available at http://www.nice.org.uk/Guidance/TA200/Costing accessed on 17July 2014

Table 4.2: Cost assumptions

F≥2	F≥3	F=4	Cost	Justification
VTq and Transient Elastography				
True Positive	True Positive	True Positive	AVT4+ Test	TP for F4 would receive AVT4 + Test
True Positive	True Positive	False Negative	AVT4 + Test	FN for F4 would receive only AVT4 + Test
True Positive	True Positive	True Negative	AVT3 + Test	TN for F4 would receive only AVT3 + Test
True Positive	True Positive	False Positive	AVT3+ Test	FP for F4, would receive AVT3 + Test
True Positive	False Negative	True Positive	AVT4+ Test	TP for F4 would receive AVT4 + Test
True Positive	False Negative	False Negative	AVT4 + Test	FN for F4 would receive only AVT4 + Test
True Positive	False Negative	True Negative	AVT3 + Test	TN for F4 would receive only AVT3 + Test
True Positive	False Negative	False Positive	AVT3+ Test	FP for F4, would receive AVT3 + Test
True Positive	True Negative		Test	TN forF≥3 would receive only theTest
True Positive	False Positive	Misclassfied Fibrosis(F=3)	AVT3+ Test	Misclassfied Fibrosis(F3), would receive AVT3+ Test
True Positive	False Positive	Misclassfied Fibrosis(F=4)	AVT4 + Test	Misclassfied Fibrosis(F4), would receive AVT4+ Test
False Negative [a]	True Positive	True Positive	AVT4+ 2Test	TP for F4 would receive AVT4 + 2 Tests
False Negative [a]	True Positive	False Negative	AVT4 + 2Test	FN for F4 would receive only AVT4+ 2 Tests
False Negative [a]	True Positive	True Negative	AVT3 + 2Test	TN for F4 would receive only AVT3 + 2 Tests
False Negative [a]	True Positive	False Positive	AVT3+ 2Test	FP for F4, would receive AVT3 + 2 Tests
False Negative [a]	False Negative	True Positive	AVT4+ 2Test	TP for F4 would receive AVT4 + 2 Tests
False Negative [a]	False Negative	False Negative	AVT4 + 2Test	FN for F4 would receive only AVT4+ 2 Tests
False Negative [a]	False Negative	True Negative	AVT3 + 2Test	TN for F4 would receive only AVT3 + 2 Tests
False Negative [a]	False Negative	False Positive	AVT3+ 2Test	FP for F4, would receive AVT3 + 2 Tests
False Negative [a]	True Negative		2Test	TN forF≥3 would receive only 2 Tests
False Negative [a]	False Positive	Misclassfied Fibrosis(F=3)	AVT3 + 2Test	Misclassfied Fibrosis(F3), would receive AVT3+ Test
False Negative [a]	False Positive	Misclassfied Fibrosis(F=4)	AVT4 + 2Test	Misclassfied Fibrosis(F4), would receive AVT4+ Test
True Negative			Test	TN forF≥2 would receive only Test
False Positive	Misclassfied Fibrosis(F=2)		Test	Misclassfied Fibrosis(F2), would receive only Test
False Positive	Misclassfied Fibrosis(F=3)		AVT3 + Test	Misclassfied Fibrosis(F3), would receive AVT3+ Test
False Positive	Misclassfied Fibrosis(F=4)		AVT4 + Test	Misclassfied Fibrosis(F4), would receive AVT4+ Test
Liver Biopsy				
True Positive	True Positive	True Positive	AVT4 + Test	TP for F4 would receive AVT4 + Test
True Positive	True Positive	True Negative	AVT3 + Test	TN for F4 would receive only AVT3 + Test
True Positive	True Negative		Test	TN forF≥3 would receive only the Test
True Negative			Test	TN forF≥2 would receive only Test

a. False negative will be diagnosed as true positives within 1 year, with an additional test.

Results

Base-case estimate

The expected costs per patient for VTq and the comparators in a scenario where a compatible Siemens ultrasound machine is required to be purchased with the VTq software are presented in table 4.3. When compared against TE, the VTq strategy generates a cost savings of £53. On the other hand, when compared against liver biopsy, the VTq strategy generates cost savings of £434.

Table 4.3: Expected cost and savings of technology and comparators (without compatible Siemens ultrasound machine)

	Expected Cost(Base-case)
Vtq	£1,971
Transient Elastography(TE)	£2,025
Liver Biopsy(LB)	£2,405
Vtq Cost Savings against TE	£53
Vtq Cost Savings against LB	£434

In a scenario where a compatible Siemens ultrasound machine is already available (with cost for Acuson machine excluded), the expected costs of VTq and the comparators are presented in Table 4.4. There is only a small change (£4) in costing savings for VTq against TE (£57) and liver biopsy (£438) when compared to a scenario without a compatible Siemens ultrasound machine. In both scenarios, VTq provides cost savings against the comparator, particularly when compared against liver biopsy.

Table 4.4: Expected cost and savings of technology and comparators (with compatible Siemens ultrasound machine)

	Expected Cost(Base-case)
Vtq	£1,968
Transient Elastography(TE)	£2,025
Liver Biopsy(LB)	£2,405
Vtq Cost Savings against TE	£57
Vtq Cost Savings against LB	£438

Sensitivity Analysis

In the deterministic sensitivity analysis, a number of variables with uncertainty were varied. The variables included in the sensitivity analysis included: i) prevalence; ii) sensitivity and specificity for VTq and TE; iii) false positive misclassification distribution (F=2 and F=3); iv) unit cost of VTq and TE tests; and v) antiviral therapy cost for F3 and F4. The results are presented in Table 4.5-4.12.

Table 4.5: Sensitivity Analysis - Prevalence

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
Prevalence(F≥2)	0.55	0.42	0.67
Vtq	£1,971	£1,925	£2,018
Transient Elastography(TE)	£2,025	£1,993	£2,056
Liver Biopsy(LB)	£2,405	£2,405	£2,405
Vtq Cost Savings against TE	£53	£69	£39
Vtq Cost Savings against LB	£434	£481	£388

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
Prevalence(F≥3)	0.40	0.32	0.49
Vtq	£1,971	£1,796	£2,158
Transient Elastography(TE)	£2,025	£1,848	£2,214
Liver Biopsy(LB)	£2,405	£2,188	£2,637
Vtq Cost Savings against TE	£53	£52	£55
Vtq Cost Savings against LB	£434	£392	£479

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
Prevalence(F=4)	0.23	0.18	0.29
Vtq	£1,971	£1,825	£2,144
Transient Elastography(TE)	£2,025	£1,879	£2,198
Liver Biopsy(LB)	£2,405	£2,260	£2,578
Vtq Cost Savings against TE	£53	£53	£53
Vtq Cost Savings against LB	£434	£435	£434

Table 4.6: Sensitivity Analysis-FP misclassification distribution

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
FP Misclassification Distribution (F=2)	0.75	0.60	0.90
Vtq	£1,971	£2,020	£1,920
Transient Elastography(TE)	£2,025	£2,099	£1,947
Liver Biopsy(LB)	£2,405	£2,405	£2,405
Vtq Cost Savings against TE	£53	£79	£27
Vtq Cost Savings against LB	£434	£386	£485

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
FP Misclassification Distribution (F=3)	0.75	0.60	0.90
Vtq	£1,971	£1,981	£1,961
Transient Elastography(TE)	£2,025	£2,034	£2,015
Liver Biopsy(LB)	£2,405	£2,405	£2,405
Vtq Cost Savings against TE	£53	£53	£54
Vtq Cost Savings against LB	£434	£424	£444

Table 4.7: Sensitivity Analysis- VTq sensitivity

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
VTq Sensitivity (F≥2)	77.01	68.88	83.52
Vtq	£1,971	£1,972	£1,971
Transient Elastography(TE)	£2,025	£2,025	£2,025
Liver Biopsy(LB)	£2,405	£2,405	£2,405
Vtq Cost Savings against TE	£53	£53	£54
Vtq Cost Savings against LB	£434	£433	£435

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
VTq Sensitivity (F≥3)	85.76	75.94	91.99
Vtq	£1,971	£1,971	£1,971
Transient Elastography(TE)	£2,025	£2,025	£2,025
Liver Biopsy(LB)	£2,405	£2,405	£2,405
Vtq Cost Savings against TE	£53	£53	£53
Vtq Cost Savings against LB	£434	£434	£434

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
VTq Sensitivity (F=4)	85.03	80.59	88.60
Vtq	£1,971	£1,971	£1,971
Transient Elastography(TE)	£2,025	£2,025	£2,025
Liver Biopsy(LB)	£2,405	£2,405	£2,405
Vtq Cost Savings against TE	£53	£53	£53
Vtq Cost Savings against LB	£434	£434	£434

Table 4.8: Sensitivity Analysis- VTq specificity

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
VTq Specificity (F≥2)	81.07	75.83	85.39
Vtq	£1,971	£1,995	£1,952
Transient Elastography(TE)	£2,025	£2,025	£2,025
Liver Biopsy(LB)	£2,405	£2,405	£2,405
Vtq Cost Savings against TE	£53	£30	£73
Vtq Cost Savings against LB	£434	£411	£453

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
VTq Specificity (F≥3)	84.36	80.69	87.45
Vtq	£1,971	£1,990	£1,955
Transient Elastography(TE)	£2,025	£2,025	£2,025
Liver Biopsy(LB)	£2,405	£2,405	£2,405
Vtq Cost Savings against TE	£53	£35	£69
Vtq Cost Savings against LB	£434	£415	£450

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
VTq Specificity (F=4)	80.44	75.57	84.54
Vtq	£1,971	£1,971	£1,971
Transient Elastography(TE)	£2,025	£2,025	£2,025
Liver Biopsy(LB)	£2,405	£2,405	£2,405
Vtq Cost Savings against TE	£53	£53	£53
Vtq Cost Savings against LB	£434	£434	£434

Table 4.9: Sensitivity Analysis- TE sensitivity

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
TE Sensitivity (F≥2)	76.16	63.89	85.22
Vtq	£1,971	£1,971	£1,971
Transient Elastography(TE)	£2,025	£2,026	£2,023
Liver Biopsy(LB)	£2,405	£2,405	£2,405
Vtq Cost Savings against TE	£53	£55	£52
Vtq Cost Savings against LB	£434	£434	£434

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
TE Sensitivity (F≥3)	77.00	64.40	80.46
Vtq	£1,971	£1,971	£1,971
Transient Elastography(TE)	£2,025	£2,025	£2,025
Liver Biopsy(LB)	£2,405	£2,405	£2,405
Vtq Cost Savings against TE	£53	£53	£53
Vtq Cost Savings against LB	£434	£434	£434

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
TE Sensitivity (F=4)	79.43	55.69	92.22
Vtq	£1,971	£1,971	£1,971
Transient Elastography(TE)	£2,025	£2,025	£2,025
Liver Biopsy(LB)	£2,405	£2,405	£2,405
Vtq Cost Savings against TE	£53	£53	£53
Vtq Cost Savings against LB	£434	£434	£434

Table 4.10: Sensitivity Analysis- TE specificity

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
TE Specificity (F≥2)	71.11	61.17	79.36
Vtq	£1,971	£1,971	£1,971
Transient Elastography(TE)	£2,025	£2,069	£1,988
Liver Biopsy(LB)	£2,405	£2,405	£2,405
Vtq Cost Savings against TE	£53	£98	£17
Vtq Cost Savings against LB	£434	£434	£434

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
TE Specificity (F≥3)	85.00	75.27	91.60
Vtq	£1,971	£1,971	£1,971
Transient Elastography(TE)	£2,025	£2,075	£1,991
Liver Biopsy(LB)	£2,405	£2,405	£2,405
Vtq Cost Savings against TE	£53	£103	£20
Vtq Cost Savings against LB	£434	£434	£434

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
TE Specificity (F=4)	83.82	77.81	88.45
Vtq	£1,971	£1,971	£1,971
Transient Elastography(TE)	£2,025	£2,025	£2,025
Liver Biopsy(LB)	£2,405	£2,405	£2,405
Vtq Cost Savings against TE	£53	£53	£53
Vtq Cost Savings against LB	£434	£434	£434

Table 4.11: Sensitivity Analysis- Test cost

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
VTq test cost	15.24	11.98	25.9
Vtq	£1,971	£1,968	£1,983
Transient Elastography(TE)	£2,025	£2,025	£2,025
Liver Biopsy(LB)	£2,405	£2,405	£2,405
Vtq Cost Savings against TE	£53	£57	£41
Vtq Cost Savings against LB	£434	£438	£422

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
TE test cost	25.9	16.19	42.06
Vtq	£1,971	£1,971	£1,971
Transient Elastography(TE)	£2,025	£2,014	£2,043
Liver Biopsy(LB)	£2,405	£2,405	£2,405
Vtq Cost Savings against TE	£53	£42	£72
Vtq Cost Savings against LB	£434	£434	£434

Table 4.12: Sensitivity Analysis- Antiviral treatment cost

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
Antiviral treatment cost (F=3) (20% Change)	2,808	2,246	3,370
Vtq	£1,971	£1,858	£2,084
Transient Elastography(TE)	£2,025	£1,908	£2,141
Liver Biopsy(LB)	£2,405	£2,309	£2,501
Vtq Cost Savings against TE	£53	£50	£57
Vtq Cost Savings against LB	£434	£451	£417

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
Antiviral treatment cost (F=4) (20% Change)	5,680	4,544	6,816
Vtq	£1,971	£1,693	£2,249
Transient Elastography(TE)	£2,025	£1,742	£2,307
Liver Biopsy(LB)	£2,405	£2,145	£2,666
Vtq Cost Savings against TE	£53	£49	£58
Vtq Cost Savings against LB	£434	£451	£417

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
Antiviral treatment cost (F=3) (50% Change)	2,808	1,404	4,212
Vtq	£1,971	£1,689	£2,254
Transient Elastography(TE)	£2,025	£1,734	£2,316
Liver Biopsy(LB)	£2,405	£2,166	£2,645
Vtq Cost Savings against TE	£53	£45	£62
Vtq Cost Savings against LB	£434	£477	£391

	Expected Cost(Base-case)	Expected Cost(Low)	Expected Cost(High)
Antiviral treatment cost (F=4) (50% Change)	5,680	2,840	8,520
Vtq	£1,971	£1,277	£2,666
Transient Elastography(TE)	£2,025	£1,318	£2,731
Liver Biopsy(LB)	£2,405	£1,753	£3,057
Vtq Cost Savings against TE	£53	£41	£66
Vtq Cost Savings against LB	£434	£477	£391

Sensitivity analysis results show that none of the variables alter the conclusion that VTq is cost-saving compared to TE and to liver biopsy. Only a few variables showed changes in expected cost per patient, therefore impacting the potential cost savings. These variables include: i) liver fibrosis overall prevalence (Metavir score F≥2); ii) false positive misclassification distribution (Metavir score F=2); iii) VTq and TE specificity for liver fibrosis stages F≥2 and F≥3; iv) VTq and TE test unit cost; and v) antiviral treatment costs, which were considered as the important cost drivers of the model.

Limitations

Data in the studies included in the meta-analysis presented limitations for modelling purposes. Ideally, the cost model should have had prevalence, sensitivity and specificity for the different liver fibrosis stages presented separately. This would have helped develop a much more robust model. Due to data limitations, the EAC had to develop a sequential model, similar to the one submitted by the sponsor, addressing some of the issues with the sponsor's submission.

Due to further non-availability of combined data for hepatitis C and hepatitis B, the results for liver fibrosis F≥3 were taken from hepatitis C studies and applied to the cost model. The test unit costs were based on a bottom-up approach undertaken by the sponsor and based on assumptions, resulting in uncertainty. However, this issue was minimised as a sensitivity analysis of the test unit costs was undertaken and found no significant influence on the cost savings achieved by the technology.

4.7 Conclusions on the economic evidence

The EAC did not find any published evidence on the technology, substantiating the conclusion reached by the sponsor that no economic evidence is available for the technology. There are studies available for TE compared to liver biopsy, which show cost savings for TE. The EAC agreed with the modelling approach adopted by the sponsor but concluded that the model could be improved to address issues related to specific assumptions used in the model and the model structure. The EAC sequentially remodelled the costs for the technology and comparators using prevalence, sensitivity, specificity, test costs and antiviral treatment cost. The EAC found that the technology (VTq) offers cost savings when compared to TE and liver biopsy. The cost saving against liver biopsy was much larger than when compared to TE. Sensitivity analysis of the key variables also did not alter the cost saving conclusion of the technology (VTq).

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

Due to the changes made by the EAC in the model structure and assumptions, the cost savings of the technology and comparators were different to those submitted by the sponsor. The sponsor reported a cost savings of £10.31 per patient for VTq compared to TE and £599 per patient when compared to liver biopsy. The EAC estimated per patient savings of £53 for VTq compared to TE and £434 compared to liver biopsy, resulting in a difference of £ 42.69 for TE and £165 when compared to liver biopsy. While the differing estimates may lead to differing budgetary impacts, both the sponsor's and EAC's model reach the same overall conclusion, that VTq is a cost saving option compared to TE and liver biopsy.

5 Conclusions

The sponsor submitted clinical evidence on VTq and the comparators liver biopsy and transient elastogaphy (TE) as identified in the scope. The EAC performed a new systematic review and meta-analysis, identifying several papers which the EAC consider should have been included, and provided additional pooled estimates for prevalence, correlation, sensitivity and specificity of VTq and TE in comparison to liver biopsy for hepatitis B, hepatitis C and combined patient populations. The EAC considered that the sponsor's interpretation of the available evidence was reasonable, and provided a fair assessment of the strengths and weaknesses of the device.

The EAC also performed a new search and agrees with the sponsor that there is no published economic evidence. With the results and probabilities from the meta-analysis, the EAC revised the cost models with some changes in the assumptions. The revised sequential model addressing issues related to the sponsor's de novo model showed that VTq generates cost savings compared to TE and liver biopsy. Costs of the technology and comparators are driven by prevalence (F≥2), false positive misclassification distribution (F=2), VTq and TE specificity for F≥2 and F≥3, VTq and TE test cost and antiviral treatment costs.

6 Implications for research

Expert advisers were approached for their opinions on the applicability of the research conducted in other European countries or in Asian countries to the UK population, and whether there were differences in the technique between different ethnic groups. The EAC received three responses. The first expert adviser commented that obesity, which may be less prevalent in some Asian countries, can cause the VTq technique to have a higher level of failures and may cause the results to be more variable. Another expert adviser remarked that the German and Romanian studies may not be applicable to a UK population as the UK population with hepatitis B and hepatitis C is a worldwide, rather than a European, population. The final expert advisor commented that they consider that the study populations would be applicable

to the UK as long as they are corrected for age, BMI and other factors. These are factors highlighted earlier in this report that could not be accounted for in the EAC's meta-analysis using the current available clinical evidence and are applicable to TE as well as VTq. In light of this, the EAC believes that a study using a UK population to compare VTq, TE and liver biopsy would be beneficial, appropriately allowing for such confounding factors, potentially through suitable sub-group analysis.

References

Aoki T, Lijima H, Yoshida M, et al., (2013) Analysis of risk factors for aiming at early detection of hepatocellular carcinoma. Hepatology 58 (Suppl. 1): 958A

Attia D, Dettmer A, Bantel H, et al., (2014) Assessment of liver fibrosis in patients with autoimmune liver diseases using ARFI elastography. Journal of Hepatology 60: S420

Atzori S, Ladep N, Pasha Y, et al., (2013) Non-invasive assessment of liver fibrosis: acoustic radiation force impulse of the left lobe correlates best with Ishak histology score. Hepatology 58 (Suppl. 1): 964A

Badea R, Lupsor M, Feier D, et al., (2013) ARFI performance in the noninvasive assessment of HCV cirrhosis, compared to transient elastography and FIB score. Hepatology International 7 (Suppl. 1): S680

Bota S, Sporea I, Sirli R, et al., (2012a) ARFI elastography vs. transient elastography: which one is more influenced by high aminotransferases values. Hepatology 56 (Suppl. 1): 839A

Bota S, Sporea I, Sirli R, et al., (2012b) Is the correlation of liver stiffness assessed by acoustic radiation force impulse elastography (ARFI) influenced by the aminotransferases level? an international multicenter study. Gastroenterology 142 (Suppl. 1): S1012

Bota S, Sporea I, Sirli R, et al., (2012c) Influence of aminotransferases level on the correlation of liver stiffness by acoustic radiation force impulse (ARFI) elastography with liver fibrosis - an international multicenter study. Journal of Hepatology 56 (Suppl. 2): S35

Bota S, Herkner H, Sporea I, et al., (2013a) Meta-analysis: ARFI elastography versus transient elastography for the evaluation of liver fibrosis. Liver International 33 (8): 1138-47

Bota S, Sporea I, Sirli R, et al., (2013b) How often do we "miss" chronic hepatitis C patients with at least significant fibrosis by using acoustic radiation force impulse elastography (ARFI) cut-off values proposed by meta-analysis? Ultraschall in der Medizin 34:

Boursier J, Isselin G, Fouchard-Hubert I, et al., (2010) Acoustic radiation force impulse: a new ultrasonographic technology for the widespread noninvasive diagnosis of liver fibrosis. European Journal of Gastroenterology and Hepatology 22 (9): 1074-84

Bravo A, Sheth S and Chopra S, (2001) Liver biopsy. New England Journal of Medicine 344 (7): 495-500

Calvaruso V, Rizzo L, Cacopardo B, et al., (2010) Comparison of transient elastography (TE) and acoustic radiation force impulse (ARFI) for noninvasive staging of liver fibrosis in patients with chronic hepatitis C. Hepatology 52 (Suppl. 1): 1237A

Calvaruso V, Di Marco V, Bronte F, et al., (2013) Acoustic radiation force impulse is better than transient elasography in assessing liver fibrosis in chronic hepatitis C using collagen proportionate area as reference. Hepatology 58 (Suppl. 1): 919A

Calvaruso V, Di Marco V, Bronte F, et al., (2014a) Quantification of fibrosis in chronic hepatitis C: performance of transient elastography and acoustic radiation force impulse using collagen proportionate area as reference. Journal of Hepatology 60: S415

Calvaruso V, Di Marco V, Bronte F, et al., (2014b) Quantification of fibrosis in chronic hepatitis C: performance of transient elastography and acoustic radiation force impulse using collagen proportionate as a reference. Digestive and Liver Disease 46: e58

Canavan C, Eisenburg J, Meng L, et al., (2013) Ultrasound elastography for fibrosis surveillance is cost effective in patients with chronic hepatitis C virus in the UK. Digestive Diseases and Sciences 58 (9): 2691-704

Carlson JJ, Kowdley KV, Sullivan SD, et al., (2009) An evaluation of the potential cost-effectiveness of non-invasive testing strategies in the diagnosis of significant liver fibrosis. Journal of Gastroenterology and Hepatology 24 (5): 786-91

Cassinotto C, Lapuyade B, Ait-Ali A, et al., (2013a) Liver fibrosis: noninvasive assessment with acoustic radiation force impulse elastography--comparison with FibroScan M and XL probes and FibroTest in patients with chronic liver disease. Radiology 269 (1): 283-92

Cassinotto C, Vergniol J, Lapuyade B, et al., (2013b) Assessment of liver fibrosis with ARFI: Comparison with M and XL probles of Fibroscan and FibroTest in chronic liver diseases. Hepatology International 7 (Suppl. 1): S487

Chen SH, Li YF, Lai HC, et al., (2012) Effects of patient factors on noninvasive liver stiffness measurement using acoustic radiation force impulse elastography in patients with chronic hepatitis C. BMC Gastroenterology 12: 105

Cramp M, (2010) Hepatitis C. [Accessed on 17th July 2014] http://www.britishlivertrust.org.uk/liver-information/liver-conditions/hepatitis-c/

Curtis L, (2013) Unit costs of health and social care 2013. [Accessed on 16/7/2013] http://www.pssru.ac.uk/project-pages/unit-costs/2013/

D'Onofrio M, Crosara S, De Robertis R, et al., (2013) Acoustic radiation force impulse of the liver. World Journal of Gastroenterology 19 (30): 4841-9

Department of Health, (2013) NHS Reference Costs 2012-2013. [Accessed on https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013

Desmond P, (2013) Out of the shadows II: Going Endemic, a national hepatitis policy update. Hepatitis B Foundation UK

Drummond M, Sculpher M, Torrance G, et al., (2005) Methods for economic health evaluation of health care programmes. 3rd ed. Oxford University Press

Forestier N, Gaus A, Herrmann E, et al., (2012) Acoustic radiation force impulse imaging for evaluation of antiviral treatment response in chronic hepatitis C. Journal of Gastrointestinal and Liver Diseases 21 (4): 367-73

Foster G and Campbell L, (2012) Hepatitis B. [Accessed on 15/07/2014] http://www.britishlivertrust.org.uk/liver-information/liver-conditions/hepatitis-b/

Foundation for Liver Research, (2004) Hepatitis B: Out of the shadows. [Accessed on 17/7/2014] http://www.liver-research.org.uk/liver-research-files/Hepatitis-B---Out-of-the-Shadows.pdf

Friedman SL, (2010) Measuring fibrogenesis in CFLD: basic and clinical aspects. Pediatric Pulmonology 45 (Suppl. 33): 121-2

Friedrich-Rust M, Wunder K, Kriener S, et al., (2009) Liver fibrosis in viral hepatitis: noninvasive assessment with acoustic radiation force impulse imaging versus transient elastography. Radiology 252 (2): 595-604

Friedrich-Rust M, Forestier N, Gaus A, et al., (2012a) Acoustic radiation force impulse imaging for evaluation of antiviral treatment response in chronic hepatitis C. Hepatology 56 (Suppl. 1): 840A

Friedrich-Rust M, Nierhoff J, Lupsor M, et al., (2012b) Performance of Acoustic Radiation Force Impulse imaging for the staging of liver fibrosis: a pooled meta-analysis. Journal of Viral Hepatitis 19 (2): e212-9

Friedrich-Rust M, Buggisch P, de Knegt RJ, et al., (2013) Acoustic radiation force impulse imaging for non-invasive assessment of liver fibrosis in chronic hepatitis B. Journal of Viral Hepatitis 20 (4): 240-7

Friedrich-Rust M, Lupsor-Platon M, de Knegt R, et al., (2014) 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. Journal of Hepatology 60 (Suppl. 1): S411-2

Frulio N, Laumonier H, Balabaud C, et al., (2009) Liver stiffness does not necessarily mean fibrosis. Hepatology 50 (Suppl. 4): 745A

Frulio N and Trillaud H, (2013) Ultrasound elastography in liver. Diagnostic and Interventional Imaging 94 (5): 515-34

Guo Y, Parthasarathy S, Goyal P, et al., (2014) Magnetic resonance elastography and acoustic radiation force impulse for staging hepatic fibrosis: a meta-analysis. Abdominal Imaging: [epub ahead of print]

Hanquinet S, Rougemont AL, Courvoisier D, et al., (2013) Acoustic radiation force impulse (ARFI) elastography for the noninvasive diagnosis of liver fibrosis in children. Pediatric Radiology 43 (5): 545-51

Harris H, Costella A, Goldberg D, et al., (2013) Hepatitis C in the UK: 2013 report.

Health Protection Agency, (2006) Migrant Health. [Accessed on 17th July 2014] http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1201767922096

Health Protection Agency, (2011) Hepatitis B in London. [Accessed on 17th July 2014] http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317137630935

Hsu S-J, Liu C-H, Kao J-H, et al., (2009) Acoustic radiation force impulse imaging predicts advanced fibrosis and cirrhosis in chronic hepatitis C patients. Hepatology 50 (Suppl. 4): 1055A-6A

Kan T, Osakabe K, Kawabe N, et al., (2013) Acoustic radiation force impulse imaging for evaluation of antiviral treatment response in chronic hepatitis C. Hepatology 58 (Suppl. 1): 1137A

Karlas T, Pfrepper C, Wiegand J, et al., (2011) 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. Scandinavian Journal of Gastroenterology 46 (12): 1458-67

Karlas T, Kollmeier J, Muller J, et al., (2013) Elastography and controlled attenuation parameter (CAP) for non-invasive graft evaluation after liver transplantation. Ultraschall in der Medizin 34:

Kudo M, Shiina T, Moriyasu F, et al., (2013) JSUM ultrasound elastography practice guidelines: liver. Journal of Medical Ultrasonics 40 (4): 325-57

Kuroda H, Kakisaka K, Tatemichi Y, et al., (2010) Non-invasive evaluation of liver fibrosis using acoustic radiation force impulse imaging in chronic hepatitis patients with hepatitis C virus infection. Hepato Gastroenterology 57 (102-103): 1203-7

Le LT, Bui LH, Le NT, et al., (2012) Comparison of liver stiffness values by virtual touch ARFI and fibroscan TE in large sample study of 554 cases. Journal of Medical Imaging and Radiation Oncology 56 (Suppl. 1): 120

Lijima H, Tanaka H, Yoshida M, et al., (2012) Usefulness of spleen stiffness measurement via virtual touch tissue quantification for prediction of liver cirrhosis. Hepatology 56 (Suppl. 1): 817A

Liu Y, Dong CF, Yang G, et al., (2014) Optimal linear combination of ARFI, transient elastography and APRI for the assessment of fibrosis in chronic hepatitis B. Liver International: [epub ahead of print]

Lupsor M, Badea R, Stefanescu H, et al., (2009) Performance of a new elastographic method (ARFI technology) compared to unidimensional transient elastography in the noninvasive assessment of chronic hepatitis C. Preliminary results. Journal of Gastrointestinal and Liver Diseases 18 (3): 303-10

Lupsor M, Badea R, Stefanescu H, et al., (2010) Performance of Acoustic Radiation Force Impulse imaging in the noninvasive assessment of liver firbosis in comparison to unidimensional transient elastography. Journal of Hepatology 52 (Suppl. 1): S165-6

Mandal PK, Goenka U, Khan EM, et al., (2011) Acoustic radiation force impulse elastography as a predictor of signfiicant fibrosis in patients with chronic liver disease. Journal of Gastroenterology and Hepatology 26 (Suppl. 5): 155

Mandal PK, Goenka U, Jha AK, et al., (2012) Acoustic radiation force impulse imaging elastography as a predictor of significant fibrosis in patients with chronic liver disease. Gastroenterology 142 (Suppl. 1): S1019

National Insitute for Health and Care Excellence, (2013) Hepatitis B (chronic): Diagnosis and management of chronic hepatitis B in children, young people and adults. NICE clinical guideline 165

National Insitute for Health and Clinical Excellence, (2010) Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C NICE technology appraisal 200

Nierhoff J, Chavez Ortiz AA, Herrmann E, et al., (2013) The efficiency of acoustic radiation force impulse imaging for the staging of liver fibrosis: a meta-analysis. European Radiology 23 (11): 3040-53

Nishikawa T, Hashimoto S, Kawabe N, et al., (2014) Factors correlating with acoustic radiation force impulse elastography in chronic hepatitis C. World Journal of Gastroenterology 20 (5): 1289-97

Noruegas M, Matos H, Gonçalves I, et al., (2012) Acoustic radiation force impulse-imaging in the assessment of liver fibrosis in children. Pediatric Radiology 42 (2): 201-4

Pendleton S and Wilson-Webb P, (2007) Rising Curve: Chronic Hepatitis B infection in the UK. Hepatitis B Foundation UK

Potthoff A, Attia D, Pischke S, et al., (2013) Influence of different frequencies and insertion depths on the diagnostic accuracy of liver elastography by acoustic radiation force impulse imaging (ARFI). European Journal of Radiology 82 (8): 1207-12

Rifai K, Bahr MJ, Mederacke I, et al., (2009) Acoustic radiation force imaging (ARFI) as a new method of ultrasonographic elastography allows accurate and flexible assessment of liver stiffness. Journal of Hepatology 50 (Suppl. 1): S88

Rizzo L, Calvaruso V, Cacopardo B, et al., (2011) Comparison of transient elastography and acoustic radiation force impulse for non-invasive staging of liver fibrosis in patients with chronic hepatitis C. American Journal of Gastroenterology 106 (12): 2112-20

Rizzo L, Nunnari G, Berretta M, et al., (2012) Acoustic Radial Force Impulse as an effective tool for a prompt and reliable diagnosis of hepatocellular carcinoma - preliminary data. European Review for Medical and Pharmacological Sciences 16 (11): 1596-8

Schneider MD, Shi Y, Sarrazin C, et al., (2013) Non-invasive assessment of liver fibrosis with acoustic radiation force imaging and transient elastography in chronic viral hepatitis. Ultraschall in der Medizin 34:

Sherman DI, Kandiah K, Jagtiani M, et al., (2012a) A "real world" controlled study of liver stiffness measured by ARFI (acoustic radiation force impulse) elastography in hospitalised patients with decompensated alcoholic liver disease (ALD): a new paradign in assessment of severity and prognosis. Gut 61 (Suppl. 2): A193

Sherman DI, Kandiah K, Sangwaiya MJ, et al., (2012b) A "real world" controlled study of liver stiffness measured by ARFI (acoustic radiation force impulse) elastography in hospitalised patients with decompensated alcoholic liver disease (ALD): a new paradign in assessment of severity and prognosis? Gastroenterology 142 (Suppl. 1): S1012

Sporea I, Sirli R, Popescu A, et al., (2010a) Acoustic radiation force impulse (ARFI)--a new modality for the evaluation of liver fibrosis. Medical Ultrasonography 12 (1): 26-31

Sporea I, Sirli R, Popescu A, et al., (2010b) The value of acoustic radiation force impulse elastography (ARFI) fro [sic] the evaluation of liver fibrosis. Journal of Hepatology 52 (Suppl. 1): S173

Sporea I, Sirli R, Popescu A, et al., (2010c) How relevant is acoustic radiation force impulse elastography (ARFI) for the evaluation of liver fibrosis? Gastroenterology 138 (Suppl. 1): S511

Sporea I, Sirli R, Popescu A, et al., (2010d) Which is the best noninvasive ultrasound method for the evaluation of liver fibrosis? Gastroenterology 138 (Suppl. 1): S511

Sporea I, Sirli R, Popescu A, et al., (2010e) Which ultrasound based method to chose for the non-invasive evaluation of liver fibrosis? Journal of Hepatology 52 (Suppl. 1): S173-4

Sporea I, Badea R, Sirli R, et al., (2011a) How efficient is acoustic radiation force impulse elastography for the evaluation of liver stiffness? Hepatitis Monthly 11 (7): 532-8

Sporea I, Sirli R, Popescu A, et al., (2011b) Can we use together transient elastgraphy (TE) and acoustic radiation force impulse elastography (ARFI) to improve fibrosis evaluation in patients with chronic HCV hepatitis? Journal of Hepatology 54 (Suppl. 1): S141

Sporea I, Sirli R, Popescu A, et al., (2011c) Is it better to use together transient elastography (TE) and acoustic radiation force impulse elastography (ARFI) for fibrosis evaluation in patients with chronic HCV hepatitis? Gastroenterology 140 (Suppl. 1): S968

Sporea I, Sirli R, Popescu A, et al., (2011d) Is it better to use two elastographic methods for liver fibrosis assessment? World Journal of Gastroenterology 17 (33): 3824-9

Sporea I, Sirli RL, Deleanu A, et al., (2011e) Acoustic radiation force impulse elastography as compared to transient elastography and liver biopsy in patients with chronic hepatopathies. Ultraschall in der Medizin 32 (Suppl. 1): S46-52

Sporea I, (2012) To biopsy or not to biopsy for the evaluation of liver fibrosis. Journal of Gastrointestinal and Liver Diseases 21 (Suppl. 1): 19-21

Sporea I, Bota S, Peck-Radosavljevic M, et al., (2012a) Acoustic radiation force impulse elastography for fibrosis evaluation in patients with chronic hepatitis C: an international multicenter study. European Journal of Radiology 81 (12): 4112-8

Sporea I, Bota S, Sirli R, et al., (2012b) Which elastographic method (transient elastography or ARFI) is more useful for liver fibrosis evaluation in patients with chronic hepatitis C? An international multicenter study. Gastroenterology 142 (Suppl. 1): S1013

Sporea I, Bota S, Sirli R, et al., (2012c) Which elastographic method (transient elastography or ARFI) is better correlated with liver fibrosis in patients with chronic hepatitis C - an international multicenter study. Journal of Hepatology 56 (Suppl. 2): S361-2

Sporea I, Jurchis A, Sirli R, et al., (2012d) ARFI elastography and supersonic shear imaging vs. transient elastography for liver fibrosis assessment. Hepatology 56 (Suppl. 1): 224A

Sporea I, Sirli R, Bota S, et al., (2012e) 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. Ultrasound in Medicine and Biology 38 (8): 1310-6

Sporea I, Bota S, Popescu A, et al., (2013a) The feasibility and value of shear-waves ultrasound based elastographic methohds for liver fibrosis evaluation (transient elastography - TE, acoustic radiation force impulse elastography - ARFI, supersonic shear imaging - SSI). Journal of Hepatology 58 (Suppl. 1): S8

Sporea I, Gilja OH, Bota S, et al., (2013b) Liver elastography - an update. Medical Ultrasonography 15 (4): 304-14

Sporea I, Gradinaru-Tascau O, Bota S, et al., (2013c) The feasibility of shear-wave elastographic methods for non-invasive assessment of liver fibrosis. Journal of Gastroenterology and Hepatology 28 (Suppl. 3): 690

Sporea I, Gradinaru-Tascau O, Bota S, et al., (2013d) The feasibility of shear-wave elastographic methods for non-invasive assessment of liver fibrosis in chronic viral hepatitis patients. Ultraschall in der Medizin 34

Stamuli E, Kruger J and Hutton J, (2009) Cost-effectiveness of ultrasound elastography in the assessment of liver fibrosis: Economic report CEP08053. [Accessed on http://nhscep.useconnect.co.uk/CEPProducts/Catalogue.aspx

Statistics OfN, (2014) Population Estimates for UK, England and Wales, Scotland and Northern Ireland, Mid-2013. [Accessed on 17th July 2014] http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/2013/index.html

Steadman R, Myers RP, Leggett L, et al., (2013) A health technology assessment of transient elastography in adult liver disease. Canadian Journal of Gastroenterology 27 (3): 149-58

Stevenson M, Lloyd-Jones M, Morgan MY, et al., (2012) 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. Health Technology Assessment 16 (4): 1-174

Whitty JA, Tallis C, Nguyen KH, et al., (2014) Cost and time savings from a rapid access model of care using transient elastography to screen and triage patients with chronic hepatitis C infection. Journal of Medical Economics 17 (2): 159-65

Yamada R, Hiramatsu N, Oze T, et al., (2014) Significance of liver stiffness measurement by acoustic radiation force impulse (ARFI) among hepatitis C patients. Journal of Medical Virology 86 (2): 241-7

Ye XP, Ran HT, Cheng J, et al., (2012) Liver and spleen stiffness measured by acoustic radiation force impulse elastography for noninvasive assessment of liver fibrosis and esophageal varices in patients with chronic hepatitis B. Journal of Ultrasound in Medicine 31 (8): 1245-53

Appendix 1: Rejected studies from Table 3.1

EAC Reference [sponsor reference]	Study	Patient population	Intervention and/or Comparator	Country	Age/gender	Study design	Comments/critique of study
Calvaruso et al. (2013)[8]	Acoustic radiation force impulse is better than transient elastography in assessing liver fibrosis in chronic hepatitis C using collagen proportionate area as reference.	hepatitis C (n=93)	VTq vs TE, LB	Italy	NA	Cross-over single centre study.	CIs reported. Not clear if study aims addressed. Abstract. **Excluded by sponsor as abstract.** **EAC rejected as different reference test to scope.**
Aoki et al. (2013)[11]	Analysis of risk factors for aiming at early detection of hepatocellular carcinoma.	Chronic Liver Disease (n= 1,203)	VTq vs TE, LB	Japan	Mean age 59.3, Male n=593	Cohort single centre study.	No CIs reported. Study aims not addressed. Abstract. **Excluded by sponsor as abstract.** **EAC rejected as unidentified study population.**
Atzori et al. (2013)[12]	Non-invasive assessment of liver fibrosis: Acoustic radiatiation force impulse of the left lobe correlates best with ishak histology score.	hepatitis B (n=11), hepatitis C (n=27), Other (n=17)	VTq vs TE, LB	United Kingdom	NA	Cross-over single centre study.	No CIs reported. Study aim/hypothesis addressed. Abstract **Excluded by sponsor as abstract.** **EAC rejected as mixed study population.**
Sporea et al. (2013d)[14]	The feasibility of shear-wave elastographic methods for non-invasive assessment of liver fibrosis in chronic viral hepatitis patients.	hepatitis B (n=67), hepatitis C (n=99)	VTq vs TE	Romania	NA	Cross-over single centre study.	No CIs reported. Study aim/hypothesis addressed. Abstract. **Excluded by sponsor as abstract.** **EAC rejected on study design.**

EAC Reference [sponsor reference]	Study	Patient population	Intervention and/or Comparator	Country	Age/gender	Study design	Comments/critique of study
Schneider et al. (2013)[17]	Non-invasive assessment of liver fibrosis with acoustic radiation force imaging and transient elastography in chronic viral hepatitis	hepatitis B (n =65), hepatitis C (n = 83)	VTq vs TE, LB	Germany	NA	Cross-over single centre study.	No CIs reported. Study aim/hypothesis addressed. Abstract. **Excluded by sponsor as abstract.** **EAC rejected for overlapping cohorts with other included references.**
Cassinotto et al. (2013b)[21]	Assessment of liver fibrosis with VTQ: Comparison with M and XL probes of Fibroscan and FibroTest in chronic liver diseases.	hepatitis B, hepatitis C, Other (n=185)	VTq vs TE, LB	France	NA	Cross-over single centre study.	No CIs reported. Study aim/hypothesis addressed. Abstract. **Excluded by sponsor as abstract.** **EAC rejected as population has mixed liver disease.**
Badea et al. (2013)[22]	VTQ performance in the noninvasive assessment of HCV cirrhosis, compared to transient elastography and FIB score.	hepatitis C (n=200)	VTq vs TE	Romania	NA	Cross-over single centre study.	No CIs reported. Study aim/hypothesis addressed. Abstract. **Excluded by sponsor as abstract.** **EAC rejected for overlapping cohorts with other included references.**
Bota et al. (2012a)[31]	VTQ elastography vs. transient elastography: Which one is more influenced by high aminotransferases values.	Total n=512. chronic hepatitis C n=357, chronic hepatitis B n=82, Other	VTq vs TE, LB	Five countries in Europe and Asia. No further details available.	51.8 ±14.4. No gender information.	Retrospective cohort, multicentre study.	Correlation between histology (liver fibrosis) and each of VTq and TE. No CIs. Aims do not fully match analysis. Abstract. **Excluded by sponsor as abstract.** **EAC rejected as population has mixed liver disease.**

EAC Reference [sponsor reference]	Study	Patient population	Intervention and/or Comparator	Country	Age/gender	Study design	Comments/critique of study
		n=73.					
Le et al. (2012)[33]	Comparison of liver stiffness values by virtual touch VTQ and fibroscan TE in large sample study of 554 cases.	Total n=554 chronic viral hepatitis n=366)	VTq vs TE	Vietnam	44±13 years Males n=353. Females n=201.	Retrospective cohort, single centre study.	No diagnostic tests, but correlation and agreement (kappa) used. CIs reported. Hypothesis not directly addressed. Prediction used but not described as such anywhere. Abstract. **Excluded by sponsor as abstract.** **EAC rejected as liver biopsy is not used as reference test.**
Sporea et al. (2012e)[34]	Comparative Study Concerning the Value of Acoustic Radiation Force Impulse Elastography (VTQ) in Comparison with Transient Elastography (TE) for the Assessment of Liver Fibrosis in Patients with Chronic Hepatitis B and C.	hepatitis B (n=53), Hepatitis C (n=107) Included in the study: hepatitis B (n=50), hepatitis C (n=96)	VTq vs TE, LB	Romania	Hep B: 39.5 ± 13.8 years Hep C: 51.4± 9 years	Retrospective cohort single center study.	Correlation of liver stiffness (histologic fibrosis), with VTq and with TE for Hepatitis C and Hepatitis B patients, were compared. Normality of data not known. Hypothesis was addressed. No CIs. Full publication. **Sponsor identified and included.** **EAC rejected as study has overlapping cohorts with another reference.**
Sporea et al. (2012b)[38]	Which elastographic method (transient elastography or VTQ) is more useful for liver fibrosis evaluation in patients with chronic	hepatitis C (n=377)	VTq vs TE, LB	Four countries. No further information.	54 years±13.2 Male n=172. Female n=2-5.	Retrospective, observational, multi-centre study.	ROC curves used for each stage of fibrosis with TE. Correlation used for both methods with histological fibrosis, and these were compared. No CIs.

EAC Reference [sponsor reference]	Study	Patient population	Intervention and/or Comparator	Country	Age/gender	Study design	Comments/critique of study
	hepatitis C? An international multicenter study.						Aims addressed. Abstract. **Excluded by sponsor as abstract. EAC rejected as paper has been published in full elsewhere.**
Freidrich-Rust et al. (2012b)[44]	Performance of Acoustic Radiation Force Impulse imaging for the staging of liver fibrosis: A pooled meta-analysis.	Mixed data available from eight studies (n=518). VTq available for n=312 hepatitis C n=222 hepatitis B n=27 Other n=59	VTq vs TE, LB	Romania (n=3), Japan (n=3), Germany (n=2)	All: 51±13years Males n=253. Females n=265. VTq: 49±13 years Male n=151. Females n=161.	Systematic review and meta – analysis of nine studies.	Area under ROC curve for VTq & different stages of diagnosis VTq & TE. Random effect meta-analytic methods with CIs reported. Hypothesis was addressed. Subgroup analysis performed for (hepatitis C, hepatitis B and NAFLD) separately. Full paper. **Sponsor identified and included. EAC rejected as study has overlapping cohorts with other references.**
Karlas et al. (2011)[45]	Acoustic radiation force impulse imaging (VTQ) for non-invasive detection of liver fibrosis: Examination standards and evaluation of interlobe differences in healthy subjects and chronic	Total n=166. Non-viral liver disease (n=47). hepatitis C (n=69). Healthy	VTq vs TE	Germany	Non-viral: 50.1±14.6 years. Male n=26. Female n=21. Hepatitis C: 50.4±38.5 years. Male n=21. Females n=48. Healthy:	Retrospective + prospective including healthy volunteers	To study the impact of different measuring sites. Good study covered an important addition: site effect and included healthy volunteers. CIs reported. Normality was assessed. Detected an effect of for different sites on mean shear wave velocity for health

EAC Reference [sponsor reference]	Study	Patient populatio n	Intervention and/or Comparator	Country	Age/gender	Study design	Comments/critique of study
	liver disease.	volunteer s (n=50).			27.8±4.0 years. Male n=21. Females n=29.		volunteers and for liver patients. Full paper. **Sponsor identified and included.** **EAC rejected as study does not use liver biopsy in the hepatitis C population.**
Sporea et al. (2011d)[47]	Is it better to use two elastographic methods for liver fibrosis assessment?	hepatitis C (n=197)	VTq vs TE, LB, and (VTq+TW)	Romania	Mean age: 50±9.8 years Male n=78, Female n=119.	Cohort study, in two centres.	CIs not reported. Aim addressed. Full journal paper. **Sponsor identified and included.** **EAC rejected as the study has an overlapping cohort with an included reference.**
Calvaruso et al. (2010)[52]	Comparison of transient elastography (TE) and acoustic radiation force impulse (VTQ) for noninvasive staging of liver fibrosis in patients with chronic hepatitis C.	hepatitis C (n=139)	VTq vs TE, LB	Italy	Not stated.	Cohort study, in two centres.	CIs not reported. Aim addressed. Missing background information. Meeting abstract. **Sponsor identified and included.** **EAC rejected as the study has an overlapping cohort with an included reference.**
Sporea et al. (2010d)[55]	Which is the best noninvasive ultrasound method for the evaluation of liver fibrosis?	Total n=71. hepatitis B (n=17), hepatitis C (n=54)	VTq vs TE, LB	Not stated.	Not stated.	Cohort study. No further information.	CIs not reported. Aim addressed. Missing background information. Meeting abstract. **Sponsor identified and included.** **EAC rejected as the study has an overlapping cohort with an included reference.**

EAC Reference [sponsor reference]	Study	Patient populatio n	Intervention and/or Comparator	Country	Age/gender	Study design	Comments/critique of study
Lupsor et al. (2009)[61]	Performance of a new elastographic method (VTQ technology) compared to unidimensional transient elastography in the noninvasive assessment of chronic hepatitis C. Preliminary results.	hepatitis C (n=112)	VTq vs TE, LB	Romania	Mean age: 48.9±12.3 years. Male n=44. Female n=68.	Cohort single centre study.	CIs reported. Aim addressed. Full journal paper. **Sponsor identified and included.** **EAC rejected as study has an overlapping cohort with an included reference.**
Lupsor et al. (2010)[57]	Performance of Acoustic Radiation Force Impulse imaging in the noninvasive assessment of liver fibrosis, in comparison to FIB4 score.	hepatitis C (n=112)	VTq vs TE, LB	Not stated.	Not stated.	Cohort study. No further information.	CIs not reported. Aim addressed. Missing background and study design information. Meeting abstract. **Excluded by sponsor as abstract.** **EAC rejected as the study contains overlapping cohorts.**
Sporea et al. (2011a)[48]	How efficient is acoustic radiation force impulse elastography for the evaluation of liver stiffness?	Total n=223. Without fibrosis n=52. With fibrosis n=171.	VTq vs TE, LB	Romania	Mean age: 48.0±13.1 years Male n=90 Female n=133	Cohort study in two centres.	CIs reported. Aim addressed. Used 38 healthy volunteers as control. Full journal paper. **Sponsor identified and included.** **EAC rejected as study has an overlapping cohort with an included reference.**
Bota et al. (2013a)[18]	Meta-analysis: VTQ elastography versus transient elastography for the evaluation of liver	Mixed (13 studies n=1,163).	VTq vs TE, LB	Not stated.	Not stated.	Meta-analysis.	CIs reported. Aim addressed. Missing background information. Full journal paper.

EAC Reference [sponsor reference]	Study	Patient population	Intervention and/or Comparator	Country	Age/gender	Study design	Comments/critique of study
	fibrosis.						**Sponsor identified and included. EAC rejected as this study includes overlapping cohorts.**
Nierhoff et al. (2013)[viii]	The efficiency of acoustic radiation force impulse-imaging for the staging of liver fibrosis: A meta-analysis.	Mixed (36 studies, n=3951)	VTq vs LB	Romania, Germany, Canada, Japan, Croatia, United States, Italy, Taiwan, Spain, Austria, Korea, England	Not stated	Meta-analysis	CIs reported Aim addressed Full journal paper **Excluded by sponsor, but included as possible evidence by EAC. Subsequently EAC rejected after further appraisal as the study includes overlapping cohorts.**

Appendix 2: Rejected studies from Table 3.2 'NA' = not available

EAC reference [sponsor reference]	Study	Subjects	Correlation in assessment of stage of liver disease and/or fibrosis using Metavir score	Sensitivity and specificity (using AUROC) in assessment of liver fibrosis	1) Use of anti-viral drugs 2) Requirement for liver biopsy	Quality of life measures	1) Hospital bed usage 2) Length of Stay	Device-related adverse events
Calvaruso et al. (2013)[8] **Excluded by sponsor as abstract. EAC rejected as different reference test to scope.**	Acoustic Radiation force impulse is better than transient elastography in assessing liver fibrosis in chronic hepatitis C using collagen proportionate area as reference	93 patients with chronic hepatitis C were evaluated for histological fibrosis using METAVIR score. All patients underwent TE and VTq.	TE and VTq significantly associated with Collagen Proportionate Area CPA (CPA-ARFI: R2 = 0.522 p<0.001; CPA-TE: R2 = 0.454 p<0.001). At multivariate logistic regression analysis, VTq was independently related to METAVIR stage F≥2 (OR:37.50 ,CI 95%:7.00-200.94, p=0.006) and METAVIR stage F4 (OR:29.87,CI95%:2.25-397.45, p=0.010).	NA	NA	NA	NA	NA
Aoki et al. (2013)[11] **Excluded by sponsor as abstract. EAC rejected as unidentified study population.**	Analysis of risk factors for aiming at early detection of hepatocellular carcinoma.	N= 1203 chronic liver disease CLD patients, who underwent VTq and total n=849 cases had Shear Wave Elastography (SWE) and total n=1717 cases had Fibroscan on the same day of liver biopsy.	VTq, fibrosis marker, tumor marker, glucose level were significantly lower in younger age in never-carc group compared to those in past/mid-carc groups (p<0.001). Liver biopsy showed significantly more number of F1/A1 cases in never-carc group, and F4/A2 cases in mid/past-carc groups (p<0.05).	NA	NA	NA	NA	NA
Atzori et al. (2013)[12] **Excluded by sponsor as abstract. EAC rejected as**	Non-invasive assessment of liver fibrosis: Acoustic radiatiation force impulse of the left	N=75 patients including hepatitis C (n=27), hepatitis B (n=11) and non-alcoholic fatty liver	Correlation with serum aminotransferase/platelets showed a statistical significance for VTq (ARFI L r=0.67; TE 0.4). In contrast, there were weak correlations with	Higher accuracy of VTq of the left lobe (ARFI L) compared to VTq measured in the right lobe (ARFI R) and TE (AUC ARFIL 0.90; ARFI R 0.74; TE 0.73).	NA	NA	NA	NA

EAC reference [sponsor reference]	Study	Subjects	Correlation in assessment of stage of liver disease and/or fibrosis using Metavir score	Sensitivity and specificity (using AUROC) in assessment of liver fibrosis	1) Use of anti-viral drugs 2) Requirement for liver biopsy	Quality of life measures	1) Hospital bed usage 2) Length of Stay	Device-related adverse events
mixed study population.	lobe correlates best with ishak histology score.	disease (n=17). VTq and TE using liver biopsy as the gold standard comparator.	necroinflammatory score (ARFI r=0.23; TE 0.26) and steatosis score (ARFI r=0.24; TE 0.32) High correlations with METAVIR scores (ARFI L r=0.63; ARFI R 0.33; TE 0.57).					
Sporea et al. (2013d)[14] **Excluded by sponsor as abstract.** **EAC rejected on study design.**	The feasibility of shear-wave elastographic methods for non-invasive assessment of liver fibrosis in chronic viral hepatitis patients.	N=172 patients with chronic viral hepatitis (hepatitis C n=99, hepatitis B n=67 and coinfection n=6). VTq, TE and Supersonic shear imaging.	Reliability of liver stiffness measurements were used. Reliable measurements between VTq and both TE and SSI were observed: 93% vs 79% (p=0.0007) and 93% vs 82% (p<0.001) respectively.	NA	NA	NA	NA	NA
Schneider et al. (2013)[17] **Excluded by sponsor as abstract.** **EAC rejected for overlapping cohorts with other included references.**	Non-invasive assessment of liver fibrosis with acoustic radiation force imaging and transient elastography in chronic viral hepatitis.	N=163 patients with chronic viral hepatitis (hepatitis C n=83, hepatitis B n=65). VTq and TE using liver biopsy as the gold standard.	VTq and TE correlate with stage of fibrosis, r>0.5 (p<0.001) for VTq and TE.	Accuracy of VTq vs TE using AUROC: F>2: 80% vs 81% F>3: 93% vs 90% F>4: 95% vs 92%. No statistical significant of AUROC between VTq and TE.	NA	NA	NA	NA
Cassinotto et al. (2013b)[21] **Excluded by sponsor as abstract.** **EAC rejected as the population has mixed liver disease.**	Assessment of liver fibrosis with VTQ: Comparison with M and XL probes of Fibroscan and FibroTest in chronic liver diseases	N=321 patients with chronic liver disease (viral hepatitis n =136; OH/NASH n=113). VTq, TE and liver biopsy.	No significant difference was found between VTq and XL probe for the diagnosis of moderate fibrosis, severe fibrosis or cirrhosis.	No significant difference was found between VTq and M probe for the diagnosis of cirrhosis (AUROC: 0.88 vs 0.91; p=0.12) or severe fibrosis (0.85 vs 0.89; =0.15) but M probe demonstrated better results for the diagnosis of moderate fibrosis (0.81 vs 0.88; p=0.008). VTq had significant	NA	NA	NA	NA

EAC reference [sponsor reference]	Study	Subjects	Correlation in assessment of stage of liver disease and/or fibrosis using Metavir score	Sensitivity and specificity (using AUROC) in assessment of liver fibrosis	1) Use of anti-viral drugs 2) Requirement for liver biopsy	Quality of life measures	1) Hospital bed usage 2) Length of Stay	Device-related adverse events
				better diagnostic performances than FibroTest for the diagnosis of cirrhosis (p=0.02).				
Badea et al. (2013)[22] **Excluded by sponsor as abstract. EAC rejected for overlapping cohorts with other includes references.**	VTQ performance in the noninvasive assessment of HCV cirrhosis, compared to transient elastography and FIB score.	N=200 chronic hepatitis C patients. VTq, TE, usual biochemical score and liver biopsy.	VTq and LS values were significantly correlated with fibrosis (r = 0.764, p<0.0001, respectively r = 0.877, p<0.0001). There is also a significant correlation between VTq and LS: (r = 0.818, p<0,0001).	AUROC for VTq vs TE vs Fib score was 0.956 vs 0.982 vs 0.953 (p=0.808) for predicting cirrhosis. The VTq with a shear wave velocity cutoff value of 1.81m/s predicted liver cirrhosis with AUROC=0.956, Se=88.89%, Sp=90.91%, PPV=84.8%, NPV=93.5%, FPR=10%, FN =11.11%, DA=89.59%.	NA	NA	NA	NA
Bota et al. (2012a)[31] **Excluded by sponsor as abstract. EAC rejected as population has mixed liver disease.**	VTQ elastography vs. transient elastography: Which one is more influenced by high aminotransferases values.	N=512 patients. To compare the influence of elevated aminotransferases level or liver stiffness (LS) values assessed by VTq & by TE. 10 valid measurements.	Overall correlation with histological fibrosis was similar for both methods: TE, r=0.646 (p<0.0001) vs. VTq, r=0.615 (p<0.0001)(comparison p=0.42).	NA	NA	NA	NA	NA
Le et al. (2012)[33] **Excluded by sponsor as abstract. EAC rejected as liver biopsy is not used as the reference test.**	Comparison of liver stiffness values by virtual touch VTQ and fibroscan TE in large sample study of 554 cases.	N=544 cases (n=366 with chronic viral hepatitis) examined by two sonologists, performing VTq and TE technique	VTq & TE values are correlated, r=0.83 (p<0.0001). However kappa was used to assess agreement between VTq & TE.: KAPPA=0.8	NA	NA	NA	NA	NA

EAC reference [sponsor reference]	Study	Subjects	Correlation in assessment of stage of liver disease and/or fibrosis using Metavir score	Sensitivity and specificity (using AUROC) in assessment of liver fibrosis	1) Use of anti-viral drugs 2) Requirement for liver biopsy	Quality of life measures	1) Hospital bed usage 2) Length of Stay	Device-related adverse events
		in the same day. VTq values compared with TE.						
Sporea et al. (2012e)[34] **Sponsor identified and included. EAC rejected as study has overlapping cohorts with another reference.**	Comparative Study Concerning the Value of Acoustic Radiation Force Impulse Elastography (VTQ) in Comparison with Transient Elastography (TE) for the Assessment of Liver Fibrosis in Patients with Chronic hepatitis B and C.	Overall n=53 hepatitis B & n=107 hepatitis C. Used in the study: n=50 hepatitis B & n=96 hepatitis C, VTq with TE Via Liver biopsy as gold standard. For VTq & TE, there were ten valid measurements per patient.	VTq with histological fibrosis: Hepatitis B: r= 0.356 (p=0.01). Hepatitis C: r= 0.490 (p <0.0001). TE with histological fibrosis: hepatitis B: r=0.403 (p=0.004). hepatitis C: r= 0.660 (p<0.0001).	NA	NA	NA	NA	NA
Sporea et al. (2012b)[38] **Excluded by sponsor as abstract. EAC rejected as paper has been published elsewhere in full.**	Which elastographic method (transient elastography or VTQ) is more useful for liver fibrosis evaluation in patients with chronic hepatitis C? An international multicenter study.	N=377 (hepatitis C). Ten measurements were performed for each patient both by TE and VTq. In each patient in the same session liver biopsy (LB) – assessed according to the Metavir score,	Correlation with histological fibrosis was not statistically significant. For TE in comparison with VTq: r=0.728(p<0.0001) vs r=0.689 (p<0.000) (p=0.28). (p=0.28 is for comparing VTq with TE correlations with LS).	VTq & TE assessed using (ROC) curves for the prediction of each stage of fibrosis: For VTq cut-offs: F>1: 1.19; F>2:1.36; F>3:1.47; F>4: 1.69. AUROC were: 0.77; 0.81; 0.86; 0.99 respectively. For TE cut-off: F>1: 5.2; F>2: 6.7; F>3: 9.6; F>4: 11.9. AUROC were: 0.77; 0.81; 0.86; 0.99, respectively. The two methods were significantly different for the	NA	NA	NA	NA

EAC reference [sponsor reference]	Study	Subjects	Correlation in assessment of stage of liver disease and/or fibrosis using Metavir score	Sensitivity and specificity (using AUROC) in assessment of liver fibrosis	1) Use of anti-viral drugs 2) Requirement for liver biopsy	Quality of life measures	1) Hospital bed usage 2) Length of Stay	Device-related adverse events
		liver stiffness (LS).		lowest cut off points (p=0.01), no difference for the following two cut off points: (p=0.77) and for the highest cut off point the difference was significant (p=0.01).				
Freidrich-Rust et al. (2012b)[44] **Sponsor identified and included. EAC rejected as study has overlapping cohorts with other references.**	Performance of Acoustic Radiation Force Impulse imaging for the staging of liver fibrosis: A pooled meta-analysis.	A systematic review.N= 518 patients from eight studies. VTq with liver biopsy. Both, VTq & TE were available for n=312 patients from four studies.	NA	AUROC was 0.87 for the diagnosis of significant fibrosis (F ≥ 2), 0.91 for the diagnosis of severe fibrosis (F ≥ 3), and 0.93 for the diagnosis of cirrhosis (F = 4). VTq & LS (Sensitivity; specificity) were: (F ≥ 2: 0.79; 0.85); (F ≥ 3: 0.86; 0.86) and (F = 4: 0.92; 0.86) for the cut-offs: F ≥ 2; F ≥ 3 and cirrhosis (F =4) respectively. Subgroup AUROC for VTq was calculated for patients with different underlying liver disease (Hep C, Hep B and Cirrhosis at 3 stages of fibrosis. The diagnostic accuracy of VTq was inferior to TE for the diagnosis of significant fibrosis (mean difference of AUROC 0.05, p=0.037) & for the diagnosis of liver cirrhosis (mean difference of AUROC 0.04, p=0.048). No significant difference but a significant heterogeneity was	NA	NA	NA	NA

EAC reference [sponsor reference]	Study	Subjects	Correlation in assessment of stage of liver disease and/or fibrosis using Metavir score	Sensitivity and specificity (using AUROC) in assessment of liver fibrosis	1) Use of anti-viral drugs 2) Requirement for liver biopsy	Quality of life measures	1) Hospital bed usage 2) Length of Stay	Device-related adverse events
				found for the diagnosis of severe fibrosis, (mean difference of AUROC 0.04, p=0.092).				
Karlas et al. (2011)[45] **Sponsor identified and included. EAC rejected as study does not use liver biopsy in the hepatitis C population**	Acoustic radiation force impulse imaging (VTQ) for non-invasive detection of liver fibrosis: Examination standards and evaluation of interlobe differences in healthy subjects and chronic liver disease.	VTq was tested in a tissue phantom and in n=50 healthy volunteers. In addition, VTq was tested in 116 patients with chronic liver disease. VTq results were compared with histological staging (non-viral liver disease) and TE. Ten valid measurements used. Measurements were performed on three different sites: i) right liver lobe through the intercostal space, ii) right liver lobe via a subcostal acoustic window in the	Biopsy was performed in the right liver lobe in 39 cases and in the left liver lobe in eight cases. Histological staging according to METAVIR was as follows: F0: n= 6, F1: n=13, F2: n=11, F3: n=4, and F4: n=13. Histological staging and VTq correlated well: (Spearman's r=0.661, p<0.001).	For the four staging Cut-off points: F0 (n=6) vs F1-4 (n=41). F0-1 (n=19) vs F2-4 (n=28). F0-2 (n=30) vs F3-4 (n=17). F0-3 (n=34) vs F4 (n=13). AUROC(95%CI) for VTq were: 0.811 (0.67-0.91), 0.827 (0.69-0.92), 0.871 (0.74-0.95) , 0.851 (0.72-0.94) Sensitivity: 78.1%,78.6%, 100%,100%. Specificity: 83.3%, 84.2%, 73.3%, 70.6%.	NA	NA	NA	NA

EAC reference [sponsor reference]	Study	Subjects	Correlation in assessment of stage of liver disease and/or fibrosis using Metavir score	Sensitivity and specificity (using AUROC) in assessment of liver fibrosis	1) Use of anti-viral drugs 2) Requirement for liver biopsy	Quality of life measures	1) Hospital bed usage 2) Length of Stay	Device-related adverse events
		medioclavicular line (in a subgroup of healthy volunteers only), and iii) left liver lobe in the epigastric region in the median line.						
Sporea et al. (2011d)[47] **Sponsor identified and included. EAC rejected as the study has an overlapping cohort with an included study.**	Is it better to use two elastographic methods for liver fibrosis assessment?	N=197 patients with chronic hepatitis C. Comparator: VTq vs TE, LB. Assessed only at baseline.	Correlation between TE and fibrosis r=0.741; between VTq and fibrosis r=0.730); and between TE and VTq r=0.675.	For significant fibrosis (F ≥ 2), TE had 77.5% Se, 86.5% Sp (AUROC 0.87). VTq had 76.9% Se and 86.7% Sp (AUROC 0.84). For predicting cirrhosis (F = 4), TE had 96.2% Se and 89.6% Sp (AUROC 0.97); VTq had 90.4% Se and 85.6% Sp (AUROC 0.91). When using both TE and VTq for predicting significant fibrosis (F ≥ 2), we obtained 60.5% Se, 93.3% Sp. For predicting cirrhosis, we obtained 84.9% Se, 94.4% Sp.	NA	NA	NA	NA
Calvaruso et al. (2010)[52] **Sponsor identified and included. EAC rejected as study has an overlapping cohort with an included reference.**	Comparison of transient elastography (TE) and acoustic radiation force impulse (VTQ) for noninvasive staging of liver fibrosis in patients with chronic hepatitis C.	N=139 patients with CHC. Comparator: VTq vs TE, LB. Assess only at baseline.	Average concordance rates of TE and VTq vs liver biopsy were 45.4% and 54.7%, respectively.	TE and VTq for predicting significant fibrosis (Metavir-F2) (AUROC 0.78), (AUROC 0.86) respectively. For severe fibrosis (Metavir-F3), (AUROC 0.83) and (AUROC 0.94). For cirrhosis TE has AUROC of 0.80 and VTq AUROC of 0.89. By pairwise comparison of AUROCs VTq is significantly	NA	NA	NA	NA

EAC reference [sponsor reference]	Study	Subjects	Correlation in assessment of stage of liver disease and/or fibrosis using Metavir score	Sensitivity and specificity (using AUROC) in assessment of liver fibrosis	1) Use of anti-viral drugs 2) Requirement for liver biopsy	Quality of life measures	1) Hospital bed usage 2) Length of Stay	Device-related adverse events
				more accurate than TE for diagnosis of significant and severe fibrosis (p = 0.024 and p = 0.002, respectively). No significant difference for diagnosis of cirrhosis (p=0.09).				
Sporea et al. (2010d)[55] **Sponsor identified and included. EAC rejected as study has an overlapping cohort with an included reference.**	Which is the best noninvasive ultrasound method for the evaluation of liver fibrosis?	N=71 subjects (n=54 with hepatitis C and n=17 with hepatitis B). Comparator: VTq vs TE, LB. Assessed only at baseline.	Linear correlation between TE and fibrosis (Spearman r=0.707, p<0.0001); Between VTq and fibrosis (rho=0.469; p<0.0001); Between TE and ARF (r=0.532, p<0.0001).	For predicting significant fibrosis (F≥2 Metavir): AUROC VTq=0.649, AUROC TE=0.731 (p=0.476); For cirrhosis (F=4 Metavir): AUROC VTq=0.868, AUROC TE= 0.936 (p=0.294)	NA	NA	NA	NA
Lupsor et al. (2009)[61] **Sponsor identified and included. EAC rejected as study has an overlapping cohort with an included reference.**	Performance of a new elastographic method (VTQ technology) compared to unidimensional transient elastography in the noninvasive assessment of chronic hepatitis C. Preliminary results.	N=112 chronic hepatitis C patients. Comparator: VTq vs TE, LB. Assessed only at baseline.	VTq with SWV is correlated only with fibrosis (r=0.717, p<0.0001) and necroinflammatory activity (r=0.328, p=0.014), but not with steatosis (r=0.122, p=0.321). There was a significant increase of shear wave velocity (ARFI) in parallel with the increase in the fibrosis stage: 1.079±0.150 (F0-F1), 1.504±0.895 (F2), 1.520±0.575 (F3), 2.552±0.782 (F4), p<0.0001, but there is a certain degree of overlap between the consecutive stages F1-F2 (p=0.072), F2-F3 (p=0.965). Shear wave velocity cut-off values (m/s) that were predictive for each fibrosis stage were: 1.19 (F≥1),	AUROC for VTq vs TE were: 0.709 vs 0.902, p=0.006 (F≥1), 0.851 vs 0.941, p=0.022 (F≥2), 0.869 vs 0.926, p=0.153 (F≥3) and 0.911 vs 0.945, p=0.331 (F4).	NA	NA	NA	NA

EAC reference [sponsor reference]	Study	Subjects	Correlation in assessment of stage of liver disease and/or fibrosis using Metavir score	Sensitivity and specificity (using AUROC) in assessment of liver fibrosis	1) Use of anti-viral drugs 2) Requirement for liver biopsy	Quality of life measures	1) Hospital bed usage 2) Length of Stay	Device-related adverse events
			1.34 (F≥2), 1.61 (F≥3) and 2.00 (F4).					
Lupsor et al. (2010)[57] **Excluded by sponsor as abstract. EAC rejected as the study contains overlapping cohorts.**	Performance of Acoustic Radiation Force Impulse imaging in the noninvasive assessment of liver fibrosis, in comparison to unidimensional transient elastography.	N=112 chronic hepatitis C patients. Comparator: VTq vs TE, LB. Assess only at baseline.	VTq and TE scores were significantly correlated with fibrosis (r=0.717, p<0.0001 and r=0.880, p<0.0001 respectively). The cut off values for VTq (m/s) predictive of fibrosis stage were: 1.19 (F≥1), 1.34 (F≥2), 1.61 (F≥3), 2.00 (F=4). The cut off values for TE (kPa) predictive of fibrosis stage were: 5.2 (F≥1), 8.1 (F≥2), 9.6 (F≥3), 13.1 (F=4). The adjusted AUROC according to the prevalence of each fibrosis stage (VTq vs TE): F≥1: 0.709 vs 0.902, p=0.006 F≥2: 0.851 vs 0.941, p=0.022 F≥3: 0.869 vs 0.926, p=0.153 F=4: 0.911 vs 0.945, p=0.331	VTq For F≥1 with a cut off of 1.19m/s: Se= 62.07%, Sp= 85.71%, PPV=96.4%, NPV=26.7%, DA=64.70%, AUROC=0.725 For F≥2 with a cut off of 1.34m/s: Se= 67.80%, Sp= 92.86%, PPV=93.0%, NPV=67.2%, DA=77.45%, AUROC=0.869 For F≥3 with a cut off of 1.61m/s: Se=79.07%, Sp= 94.83%, PPV=91.9%, NPV=85.9%, DA=89.21%, AUROC=0.900 For F≥4 with a cut off of 2.00m/s: Se= 80.00%, Sp= 95.45%, PPV=90.3%, NPV=90.0%, DA=90.19%, AUROC=0.936 TE For F≥1 with a cut off of 5.2kPa: Se= 85.26%, Sp= 92.86%, PPV=98.8%, NPV=48.1%, DA=86.36%, AUROC=0.918 For F≥2 with a cut off of 8.1kPa: Se=84.85%, Sp= 92.35%, PPV=96.6%, NPV=80.4%, DA=88.18%, AUROC=0.961	NA	NA	NA	NA

EAC reference [sponsor reference]	Study	Subjects	Correlation in assessment of stage of liver disease and/or fibrosis using Metavir score	Sensitivity and specificity (using AUROC) in assessment of liver fibrosis	1) Use of anti-viral drugs 2) Requirement for liver biopsy	Quality of life measures	1) Hospital bed usage 2) Length of Stay	Device-related adverse events
				For F≥3 with a cut off of 9.6kPa: Se= 95.83%, Sp= 86.89%, PPV=85.2%, NPV=96.4%, DA=90%, AUROC=0.957 For F=4 with a cut off of 13.1kPa: Se= 95.12%, Sp= 89.17%, PPV=84.8%, NPV=96.8%, DA=90.90%, AUROC=0.970				
Sporea et al. (2011a)[48] **Sponsor identified and included. EAC rejected as study has an overlapping cohort with an included reference.**	How efficient is acoustic radiation force impulse elastography for the evaluation of liver stiffness?	223 subjects; n=52 without fibrosis (n=38 healthy volunteers and n=14 patients with F0 on LB), n=36 with F1, n=40 with F2, n=26 with F3 and n=69 with liver cirrhosis (n=46 with LB and n=23 with signs of cirrhosis). Comparator: VTq vs TE, LB. Assessed only at	A strong linear correlation (Spearman rho = 0.870) between TE and fibrosis (p < 0.0001); a weaker correlation between VTq and fibrosis (Spearman rho = 0.646; p<0.0001). TE was also correlated with VTq (Spearman rho = 0.733, p<0.0001). From n=162 patients for whom LB was performed, n=14 (8.6%) had no fibrosis (F0), n=36 (22.2%) had mild fibrosis (F1), n=40 (24.7%) had significant fibrosis (F2), n=26 (16%) had severe fibrosis (F3), and n=46 (28.4%) had cirrhosis (F4), according to the Metavir scoring system.	For predicting significant fibrosis (F ≥ 2), TE with a cut-off of 7.1 kPa has AUROC 0.953; VTq with a cut-off of 1.27 m/s has AUROC 0.890, sensitivity (Se) of 88.7%, specificity (Sp) of 67.5%, positive predictive value (PPV) of 64.5%, and negative predictive value (NPV) of 90% (p= 0.0044). For predicting cirrhosis (F=4), the optimum cut-off values were 14.4 kPa for TE (AUROC: 0.985, Se: 95.6%, Sp: 94.7%, PPV: 89.2%, NPV: 98%) and 1.7 m/s. For VTq (AUROC: 0.931, Se: 93%, Sp: 86.7%, PPV: 73.6%, NPV: 96.9%)	NA	NA	NA	NA

EAC reference [sponsor reference]	Study	Subjects	Correlation in assessment of stage of liver disease and/or fibrosis using Metavir score	Sensitivity and specificity (using AUROC) in assessment of liver fibrosis	1) Use of anti-viral drugs 2) Requirement for liver biopsy	Quality of life measures	1) Hospital bed usage 2) Length of Stay	Device-related adverse events
		baseline.		(p= 0.0102).				
Bota et al. (2013a)[18] **Sponsor identified and included. EAC rejected as this study includes overlapping cohorts.**	Meta-analysis: VTQ elastography versus transient elastography for the evaluation of liver fibrosis.	Thirteen studies (Eleven full-length articles and two abstracts) including n=1163 patients with chronic hepatopathies (mixed). Comparator: VTq vs TE, LB. Assessed only at baseline.	NA	For detection of significant fibrosis, (F ≥ 2) summary sensitivity (Se) was 0.74 (95% CI: 0.66–0.80) and specificity (Sp) was 0.83 (95% CI: 0.75–0.89) for VTq; while for TE the Se was 0.78 (95% CI: 0.72–0.83) and Sp was 0.84 (95% CI: 0.75–0.90). For cirrhosis, the summary Se was 0.87 (95% CI: 0.79–0.92) and Sp was 0.87 (95% CI: 0.81–0.91) for VTq, and, respectively, 0.89 (95% CI: 0.80–0.94) and 0.87 (95% CI: 0.82–0.91) for TE. The diagnostic odds ratio of VTq and TE not significant for fibrosis [mean difference in rDOR = 0.27 (95% CI: 0.69–0.14)] and cirrhosis [mean difference in rDOR = 0.12 (95% CI: 0.29–0.52)].	LB used as gold standard	NA	NA	NA
Nierhoff et al. (2013)[viii] **Excluded by sponsor, but included as possible evidence by EAC. Subsequently EAC rejected after further appraisal as the**	The efficiency of acoustic radiation force impulse-imaging for the staging of liver fibrosis: A meta-analysis.	36 studies (comprised of 21 full-length articles and 15 abstracts) including n=3951 patients with chronic hepatopathies (mixed)	NA	AUROC for VTq: F≥2: 0.84 (95% CI, 0.80-0.87) F≥3: 0.89 (95% CI, 0.87-0.92) F=4: 0.91 (95% CI, 0.89-0.94) For F≥3 some of the heterogeneity may be explained by patients with hepatitis B: AUROC including hepatitis B:	NA	NA	NA	NA

EAC reference [sponsor reference]	Study	Subjects	Correlation in assessment of stage of liver disease and/or fibrosis using Metavir score	Sensitivity and specificity (using AUROC) in assessment of liver fibrosis	1) Use of anti-viral drugs 2) Requirement for liver biopsy	Quality of life measures	1) Hospital bed usage 2) Length of Stay	Device-related adverse events
study includes overlapping cohorts.		Comparator: VTq vs LB.		0.87 (95% CI, 0.85-0.90) AUROC excluding hepatitis B: 0.92 (95% CI, 0.89-0.95)				

Appendix 3: Summary of key points from sponsor-excluded published studies

EAC reference [sponsor reference]	Sponsor submission reason for exclusion	EAC comments
Liu et al. (2014)[1]	Unclear	The EAC disagree with exclusion of this paper. The study population (hepatitis B)

EAC reference [sponsor reference]	Sponsor submission reason for exclusion	EAC comments
		the index, comparator and reference test fulfil the inclusion criteria. This is the only study published from this centre (Shenzhen, China).
Calvaruso et al. (2014a)[3]	Unclear	The EAC agree with exclusion of this paper based on different reference test (proportionate collagen area) and duplication of study results with Calvaruso et al. (2014b)[5]
Attia et al. (2014)[4]	Study population autoimmune disease	The EAC agree with exclusion of this paper based on study population.
Calvaruso et al. (2014b)[5]	Unclear	The EAC agree with exclusion of this paper based on different reference test (proportionate collagen area).
Sporea et al. (2013b)[6]	Update	The EAC agree with exclusion of this paper because this is a review article.
Kan et al. (2013)[7]	None by antiviral treatment	The EAC agree with exclusion of this paper based on study design. This is not a diagnostic accuracy study but monitoring response to treatment during antiviral treatment.
Calvaruso et al. (2013)[8]	Unclear	The EAC agree with exclusion of this paper based on different reference test (proportionate collagen area), and duplication of study results with Calvaruso et al. (2014b)[5].
Sporea et al. (2013c)[9]	Unclear	The EAC agree with exclusion of this paper based on study design. This is not a diagnostic accuracy study but a test repeatability investigation. No reference test.
Kudo et al. (2013)[10]	Guidelines	The EAC agree with exclusion of this paper because this is a practices guidelines article.
Aoki et al. (2013)[11]	Unclear	The EAC agree with exclusion of this paper based on study population (unidentified chronic liver disease)
Atzori et al. (2013)[12]	Unclear	The EAC agree with exclusion of this paper based on study population (mixed chronic liver disease)
Cassinotto et al. (2013a)[13]	Unclear	The EAC agree with exclusion of this paper based on study population (viral hepatitis + alcoholic/NASH disorder + other diseases).
Sporea et al. (2013d)[14]	Unclear	The EAC agree with exclusion of this paper based on study design. This is not a diagnostic accuracy study but a test repeatability investigation. No reference test.
Karlas et al. (2013)[15]	Study population and comparator	The EAC agree with exclusion of this paper based on study population (mixed) and study design (lack of biopsy)
Bota et al. (2013b)[16]	Unclear	The EAC agree with exclusion of this paper because the outcome measurements are not provided (only positive predictive value and negative predictive value are provided)
Schneider et al. (2013)[17]	Unclear	The EAC agree with exclusion of this paper because the two included population

EAC reference [sponsor reference]	Sponsor submission reason for exclusion	EAC comments
		cohorts with hepatitis C and hepatitis B have been subsequently published in full in Friedrich-Rust et al. (2013)[25] and Friedrich-Rust et al. (2014)[2].
Bota et al. (2013a)[18]	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 EAC agree with exclusion of this paper.
D'Onofrio et al. (2013)[19]	Review paper	The EAC agree with exclusion of this paper because this is a review article.
Potthoff et al. (2013)[20]	Unclear	The EAC agree with exclusion of this paper based on study design. No reference test.
Cassinotto et al. (2013b)[21]	Unclear	The EAC agree with exclusion of this paper based on study population (mixed chronic liver disease). The abstract has been subsequently published in full.
Badea et al. (2013)[22]	Unclear	The EAC agree with exclusion of this paper based because of the overlapping cohorts with later a publication, Friedrich-Rust et al. (2014)[2]
Frulio et al. (2013)[23]	Review paper	The EAC agree with exclusion of this paper because this is a review article.
Sporea et al. (2013a)[24]	Unclear	The EAC agree with exclusion of this paper based on study design. This is not a diagnostic accuracy study but a test repeatability investigation. No reference test.
Rizzo et al. (2012)[27]	Study population and comparator	The EAC agree with exclusion of this paper based on study population (unclear, hepatocellular carcinoma) and study design (lack of biopsy)
Forestier et al. (2012)[28]	Unclear	The EAC agree with exclusion of this paper based on study design. This is not a diagnostic accuracy study but response to treatment during antiviral treatment. No LB as a reference test
Sporea et al. (2012d)[29]	Unclear	The EAC agree with exclusion of this paper based on study design (lack of biopsy)
Lijima et al. (2012)[30]	Reference test	The EAC agree with exclusion of this paper. It is unclear if investigators used liver biopsy as the reference test. Furthermore this group has published their results in Sporea et al. (2012a)[26].
Bota et al. (2012a)[31]	Unclear	The EAC agree with exclusion of this paper based on study population (mixed patient cohort)
Friedrich-Rust et al. (2012a)[32]	Unclear	The EAC agree with exclusion of this paper based on study design. This is not a diagnostic accuracy study but assessment of response to treatment during antiviral treatment.

EAC reference [sponsor reference]	Sponsor submission reason for exclusion	EAC comments
Le et al. (2012)[33]	Unclear	The EAC agree with exclusion of this paper based on study design. The comparator is TE but liver biopsy is not used as a reference test.
Sherman et al. (2012a)[35]	Study population (alcoholic liver disease)	The EAC agree with exclusion of this paper based on study population (alcoholic liver disease)
Sherman et al. (2012b)[36]	Study population (alcoholic liver disease)	The EAC agree with exclusion of this paper based on study population (alcoholic liver disease)
Bota et al. (2012b)[37]	Unclear	The EAC agree with exclusion of this paper based on study population (hepatitis C, hepatitis B, non viral hepatitis) and because of the overlapping cohorts with a full publication from Sporea et al. (2012a)[26]
Sporea et al. (2012b)[38]	Unclear	The EAC agree with exclusion of this paper because it has been published in full by Sporea et al. (2012a)[26]
Mandal et al. (2012)[39]	Study population	The EAC agree with exclusion of this paper based on study population (mixed population)
Bota et al. (2012c)[40]	Study population	The EAC agree with exclusion of this paper based on study population (mixed population)
Sporea et al. (2012c)[41]	Unclear	The EAC agree with exclusion of this paper because it has been published in full by Bota et al. (2012c)[40]
Sporea (2012)[42]	Review paper	The EAC agree with exclusion of this paper because this is a review article.
Sporea (2012)[43]	Duplicate	The EAC agree with exclusion of this paper because this is a review article.
Mandal et al. (2011)[46]	Unclear	The EAC agree with exclusion of this paper based on study population (mixed population). Duplicate of sponsor reference 39
Sporea et al. (2011c)[49]	Unclear	The EAC agree with exclusion of this paper based because of the overlapping cohorts with a multiple later publications from this group.
Sporea et al. (2011b)[50]	Unclear	The EAC agree with exclusion of this paper based because of the overlapping cohorts with a multiple later publications from this group.
Sporea et al. (2011e)[51]	Study population	The EAC agree with exclusion of this paper based on study population (unidentified chronic liver disease)
Boursier et al. (2010)[53]	Study population (unclear) and reference test (fibrosis blood test)	The EAC agree with exclusion of this paper based on study population and reference test.
Friedman (2010)[54]	Review paper	The EAC agree with exclusion of this paper because this is a review article.
Sporea et al. (2010c)[56]	Duplicate	The EAC agree with exclusion of this paper based because of the overlapping cohorts with a multiple later publications from this group
Lupsor et al. (2010)[57]	Unclear	The EAC agree with exclusion of this paper based because of the overlapping

EAC reference [sponsor reference]	Sponsor submission reason for exclusion	EAC comments
		cohorts with a multiple later publications from this group
Sporea et al. (2010b)[58]	Duplicate	The EAC agree with exclusion of this paper based because of the overlapping cohorts with a multiple later publications from this group.
Sporea et al. (2010e)[59]	Duplicate	The EAC agree with exclusion of this paper based because of the overlapping cohorts with a multiple later publications from this group.
Sporea et al. (2010a)[60]	Unclear	The EAC agree with exclusion of this paper based because of the overlapping cohorts with a multiple later publications from this group.
Friedrich-Rust et al. (2009)[62]	Unclear	The EAC agree with exclusion of this paper based because of the overlapping cohorts with a multiple later publications from this group.
Rifai et al. (2009) [63]	Mixed study population	The EAC agree with exclusion of this paper based on study population (unidentified chronic liver disease)
Frulio et al. (2009)[64]	Mixed population and unclear comparator	The EAC agree with exclusion of this paper based on study population (viral hepatitis, alcoholic liver disease, cholestasis, right heart failure)
Hsu et al. (2009)[65]	Unclear comparator	The EAC agree with exclusion of this paper based on unclear reference test.

Appendix 4: Clinical evidence search strategy

Ovid Medline(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; Searched on 10th July 2014, and Embase 1980 to 10th July 2014

1	virtual touch tissue quantification.mp.	147
2	acoustic radiation force impulse.mp.	990
3	acoustic radiation force impulse imaging.mp.	520
4	acoustic radiation force impulse elastography.mp.	158
5	ARFI elastography.mp.	201
6	elasticity imaging techniques.mp. or Elasticity Imaging Techniques/	9012
7	liver diseases.mp. or Liver Diseases/	170252
8	liver fibrosis.mp. or Liver Cirrhosis/	168289
9	Hepatitis/ or Hepatitis B, Chronic/ or Hepatitis, Viral, Human/ or Hepatitis B/ or Hepatitis C/ or Hepatitis C, Chronic/ or hepatitis.mp.	469924
10	prognosis.mp. or Prognosis/	1071074
11	predictive.mp. or "Predictive Value of Tests"/	559008
12	receiver operating characteristic.mp. or ROC Curve/	100654
13	adverse event.mp.	35527
14	"Sensitivity and Specificity"/ or diagnostic accuracy.mp.	647660
15	antiviral.mp. or Antiviral Agents/	209075
16	quality of life.mp. or "Quality of Life"/	507828
17	1 or 2 or 3 or 4 or 5 or 6	9406
18	7 or 8 or 9	697146
19	10 or 11 or 12 or 13 or 14 or 15 or 16	2800715
20	17 and 18 and 19	1983
21	limit 20 to english language	1855
22	limit 21 to yr="2009 -Current"	1680
23	limit 22 to humans	1474
24	remove duplicates from 23	1131

The Cochrane Library, to present; searched on 11th July 2014.

	Search all text	acoustic radiation force impulse
OR	Search all text	ARFI elastography
OR	Search all text	ARFI
OR	Search all text	virtual touch tissue quantification
OR	Search all text	elasticity imaging

DARE, to present; searched on 11th July 2014.

Any field	acoustic radiation force impulse	OR
Any field	virtual touch tissue quantification	OR
Any field	elasticity imaging	

Appendix 5: Summary of all EAC systematic review identified studies (n=49)

Author(s)	Title	Publication	Decision
Bota S, Sporea I, Sirli R, Popescu A, Jurchis A	Factors which influence the accuracy of acoustic radiation force impulse (ARFI) elastography for the diagnosis of liver fibrosis in patients with chronic hepatitis C.	Ultrasound in Medicine and Biology. 2013, 39(3):407-12	The EAC excludes this study as it has an overlapping patient cohort with another included study.
Bota S, Sporea I, Sirli R, Popescu A, Danila M, Jurchis A, Gradinaru-Tascau O	How often do we "miss" chronic hepatitis C patients with at least significant fibrosis by using acoustic radiation force impulse elastography (ARFI) cut-off values proposed by meta-analysis?	Ultraschall in der Medizin 2013; 34 – WS_SL1_05	The EAC excludes this meta-analysis as it overlaps other included studies and has a mixed patient cohort.
Bota S, Sporea I, Peck-Radosavljevic M, Sirli R, Tanaka H, Iijima H, et al.	The influence of aminotransferase levels on liver stiffness assessed by Acoustic Radiation Force Impulse Elastography: A retrospective multicentre study.	Digestive and Liver Disease. 2013; 45(9):762-8.	The EAC excludes this study as it has an overlapping patient cohort with another included study.
Bota S, Herkner H, Sporea I, Salzl P, Sirli R, Neghina AM, et al.	Meta-analysis: ARFI elastography versus transient elastography for the evaluation of liver fibrosis.	Liver International. 2013; 33(8):1138-47.	The EAC excludes this meta-analysis as it has an overlapping patient cohort with another included study.
Boursier J, Isselin G, Fouchard-Hubert I, Oberti F, Dib N, Lebigot J, et al.	Acoustic radiation force impulse: A new ultrasonographic technology for the widespread noninvasive diagnosis of liver fibrosis.	European Journal of Gastroenterology and Hepatology. 2010; 22(9):1074-84.	The EAC excludes this study as it has a mixed patient cohort.
Cassinotto C, Lapuyade B, Ait-Ali A, Vergniol J, Gaye D, Foucher J, et al.	Liver fibrosis: Noninvasive assessment with acoustic radiation force impulse elastography - Comparison with Fibroscan M and XL probes and FibroTest in patients with chronic liver disease.	Radiology. 2013; 269(1):283-92.	The EAC excludes this study as it has a mixed patient cohort.
Chen SH, Li YF, Lai HC, Kao JT, Peng CY, Chuang PH, et al.	Effects of patient factors on noninvasive liver stiffness measurement using acoustic radiation force impulse elastography in patients with chronic hepatitis C.	BMC Gastroenterology. 2012; 12(105).	The EAC includes this study.
Chen SH, Li YF, Lai HC, Kao JT, Peng CY,	Noninvasive assessment of liver fibrosis via	Journal of Viral Hepatitis.	The EAC excludes this study as it

Author(s)	Title	Publication	Decision
Chuang PH, et al.	spleen stiffness measurement using acoustic radiation force impulse sonoelastography in patients with chronic hepatitis B or C.	2012; 19(9):654-63.	uses spleen measurements.
Chen S, Sanchez W, Callstrom MR, Gorman B, Lewis JT, Sanderson SO, et al.	Assessment of liver viscoelasticity by using shear waves induced by ultrasound radiation force.	Radiology. 2013; 266(3):964-70.	The EAC excludes this study as it does not use VTq.
Chung JH, Ahn HS, Kim SG, Lee YN, Kim YS, Jeong SW, et al.	The usefulness of transient elastography, acoustic-radiation-force impulse elastography, and real-time elastography for the evaluation of liver fibrosis.	Clinical and molecular hepatology. 2013; 19(2):156-64.	The EAC excludes this study as it has a mixed patient cohort.
Colombo S, Buonocore M, Del Poggio A, Jamoletti C, Elia S, Mattiello M, et al.	Head-to-head comparison of transient elastography (TE), real-time tissue elastography (RTE), and acoustic radiation force impulse (ARFI) imaging in the diagnosis of liver fibrosis.	Journal of Gastroenterology. 2012; 47(4):461-9.	The EAC excludes this study as it has a mixed patient cohort.
Crespo G, Fernandez-Varo G, Marino Z, Casals G, Miquel R, Martinez SM, et al.	ARFI, FibroScan, ELF, and their combinations in the assessment of liver fibrosis: a prospective study.	Journal of hepatology. 2012; 57(2):281-7.	The EAC excludes this study as it has a mixed patient cohort.
Ebinuma H, Saito H, Komuta M, Ojiro K, Wakabayashi K, Usui S, et al.	Evaluation of liver fibrosis by transient elastography using acoustic radiation force impulse: comparison with Fibroscan.	Journal of Gastroenterology.1238; 46(10):1238-48.	The EAC exclude this study as it has anoverlapping patient cohort with another included study.
Fierbinteanu-Braticevici C, Andronescu D, Usvat R, Cretoiu D, Baicus C, Marinoschi G.	Acoustic radiation force imaging sonoelastography for noninvasive staging of liver fibrosis.	World J Gastroenterol. 2009; 15(44):5525-32.	The EAC excludes this study as it has an overlapping patient cohort with another included study.
Forestier N, Gaus A, Herrmann E, Sarrazin C, Bojunga J, Poynard T, et al.	Acoustic radiation force impulse imaging for evaluation of antiviral treatment response in chronic hepatitis C.	Journal of Gastrointestinal and Liver Diseases. 2012; 21(4):367-73.	The EAC excludes this study as it does not use liver biopsy as a comparator.
Friedrich-Rust M, Ong M, Martens S, Sarrazin C, Bojunga J, Zeuzem S, et al.	Performance of Transient Elastography for the Staging of Liver Fibrosis: A Meta-Analysis.	Gastroenterology. 2008; 134(4):960-74.e8.	The EAC excludes this meta-analysis as it overlaps other included studies and has a mixed patient cohort.
Friedrich-Rust M, Wunder K, Kriener S, Sotoudeh F, Richter S, Bojunga J, et al.	Liver fibrosis in viral hepatitis: Noninvasive assessment with acoustic radiation force impulse imaging versus transient	Radiology. 2009; 252(2):595-604.	The EAC excludes this study as it has anoverlapping patient cohort with another included study.

Author(s)	Title	Publication	Decision
	elastography.		
Friedrich-Rust M, Lupsor-Platon M, De Knegt R, Dries V, Buggisch P, Gebel M, et al.	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.	Journal of Hepatology. 2014; 60(1):S411-S2.	The EAC includes this study. The sponsor also identified this study.
Friedrich-Rust M, Buggisch P, De Knegt RJ, Dries V, Shi Y, Matschenz K, et al.	Acoustic radiation force impulse imaging for non-invasive assessment of liver fibrosis in chronic hepatitis B.	Journal of Viral Hepatitis. 2013; 20(4):240-7.	The EAC includes this study. The sponsor also identified this study.
Goertz RS, Zopf Y, Jugl V, Heide R, Janson C, Strobel D, et al.	Measurement of liver elasticity with acoustic radiation force impulse (ARFI) technology: an alternative noninvasive method for staging liver fibrosis in viral hepatitis.	Ultraschall in der Medizin. 2010; 31(2):151-5.	The EAC excludes this study as it does not use the METAVIR scoring system.
Goertz RS, Sturm J, Zopf S, Wildner D, Neurath MF, Strobel D.	Outcome analysis of liver stiffness by ARFI (acoustic radiation force impulse) elastometry in patients with chronic viral hepatitis B and C.	Clin Radiol. 2014; 69(3):275-9.	The EAC excludes this study as it does not use the METAVIR scoring system.
Goertz RS, Sturm J, Pfeifer L, Wildner D, Wachter DL, Neurath MF, et al.	ARFI cut-off values and significance of standard deviation for liver fibrosis staging in patients with chronic liver disease.	Annals of Hepatology. 2013; 12(6):935-41.	The EAC excludes this study as it does not use the METAVIR scoring system.
Guo Y, Parthasarathy S, Goyal P, McCarthy R, Larson A, Miller F.	Magnetic resonance elastography and acoustic radiation force impulse for staging hepatic fibrosis: a meta-analysis.	Abdominal Imaging. 2014 e-pub ahead of print	The EAC excludes this meta-analysis as it overlaps with other included studies and has a mixed patient cohort.
Hanquinet S, Rougemont AL, Courvoisier D, Rubbia-Brandt L, McLin V, Tempia M, et al.	Acoustic radiation force impulse (ARFI) elastography for the noninvasive diagnosis of liver fibrosis in children.	Pediatric Radiology. 2013; 43(5):545-51.	The EAC excludes this study as it has a mixed patient cohort.
Haque M, Robinson C, Owen D, Yoshida EM, Harris A.	Comparison of acoustic radiation force impulse imaging (ARFI) to liver biopsy histologic scores in the evaluation of chronic liver disease: A pilot study.	Annals of Hepatology. 2010; 9(3):289-93.	The EAC excludes this study as it has a mixed patient cohort.
Joo SK, Kim W, Kim HY, Kim BG, Kim DH.	Prospective comparison of noninvasive fibrosis assessment to predict advanced	Hepatology International. 2014; 8(1):S198.	The EAC excludes this study as the available abstract does not provide

Author(s)	Title	Publication	Decision
	fibrosis or cirrhosis in Asian patients with hepatitis C.		sufficient ARFI results.
Karlas T, Pfrepper C, Wiegand J, Wittekind C, Neuschulz M, Mossner J, et al.	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.	Scandinavian Journal of Gastroenterology. 2011; 46(12):1458-67.	The EAC excludes this study as it has a mixed patient cohort.
Kircheis G, Sagir A, Vogt C, Vom Dahl S, Kubitz R, Haussinger D.	Evaluation of acoustic radiation force impulse imaging for determination of liver stiffness using transient elastography as a reference.	World Journal of Gastroenterology. 2012; 18(10):1077-84.	The EAC excludes this study as it has a mixed patient cohort.
Kuroda H, Kakisaka K, Tatemichi Y, Sawara K, Miyamoto Y, Oikawa K, et al.	Non-invasive evaluation of liver fibrosis using acoustic radiation force impulse imaging in chronic hepatitis patients with hepatitis C virus infection.	Hepato Gastroenterology. 2010; 57(102-103):1203-7.	The EAC includes this study.
Lachtara M, Laurans L, Wawrzynowicz-Syczewska M, Mietkiewski J, Jurczyk K.	Quantitative shear wave ultrasound elastography: A new, non-invasive method for liver fibrosis staging in patients with chronic hepatitis C.	Experimental and Clinical Hepatology. 2012; 8(3-4):13-6.	The EAC excludes this study as it does not use VTq.
Liu Y, Dong CF, Yang G, Liu J, Yao S, Li HY, et al.	Optimal linear combination of ARFI, transient elastography and APRI for the assessment of fibrosis in chronic hepatitis B.	Liver Int. 2014 e-pub ahead of print	The EAC includes this study.
Lupsor M, Badea R, Stefanescu H, Sparchez Z, Branda H, Serban A, et al.	Performance of a new elastographic method (ARFI technology) compared to unidimensional transient elastography in the noninvasive assessment of chronic hepatitis C. Preliminary results.	Journal of Gastrointestinal and Liver Diseases. 2009; 18(3):303-10.	The EAC excludes this study as it has an overlapping patient cohort with another study.
Nishikawa T, Hashimoto S, Kawabe N, Harata M, Nitta Y, Murao M, et al.	Factors correlating with acoustic radiation force impulse elastography in chronic hepatitis C.	World Journal of Gastroenterology. 2014; 20(5):1289-97.	The EAC includes this study.
Piscaglia F, Salvatore V, Di Donato R, D'Onofrio M, Gualandi S, Gallotti A, et al.	Accuracy of VirtualTouch Acoustic Radiation Force Impulse (ARFI) imaging for the diagnosis of cirrhosis during liver	Ultraschall in der Medizin. 2011; 32(2):167-75.	The EAC excludes this study as it has an overlapping patient cohort with another included study.

Author(s)	Title	Publication	Decision
	ultrasonography		
Ricci P, Marigliano C, Cantisani V, Porfiri A, Marcantonio A, Lodise P, et al.	Ultrasound evaluation of liver fibrosis: preliminary experience with acoustic structure quantification (ASQ) software.	La Radiologia Medica. 2013; 118(6):995-1010.	The EAC excludes this study as it does not use VTq.
Rizzo L, Calvaruso V, Cacopardo B, Alessi N, Attanasio M, Petta S, et al.	Comparison of transient elastography and acoustic radiation force impulse for non-invasive staging of liver fibrosis in patients with chronic hepatitis C.	American Journal of Gastroenterology. 2011; 106(12):2112-20.	The EAC includes this study.
Shah A, Jaffer O, Lung P, Bosanac D, Sidhu P.	Acoustic radiation force impulse (ARFI) imaging can identify early fibrosis in viral hepatitis: Preliminary results in 83 patients compared with aspartate transaminase to platelet ratio index (APRI) and simultaneous liver biopsy.	Clinical Radiology. 2013; 68:S7.	The EAC excludes this study as it does not use the METAVIR scoring system.
Sporea I, Sirli R, Popescu A, Bota S, Badea R, Lupsor M, et al.	Is it better to use two elastographic methods for liver fibrosis assessment?	World Journal of Gastroenterology. 2011; 17(33):3824-9.	The EAC excludes this study as it has an overlapping patient cohort with another included study.
Sporea I, Badea R, Sirli R, Lupsor M, Popescu A, Danila M, et al.	How efficient is acoustic radiation force impulse elastography for the evaluation of liver stiffness?	Hepatitis Monthly. 2011; 11(7):532-8.	The EAC excludes this study as it has a mixed patient cohort.
Sporea I, Sirli R, Popescu A, Danila M.	Acoustic Radiation Force Impulse (ARFI)--a new modality for the evaluation of liver fibrosis.	Medical ultrasonography. 2010; 12(1):26-31.	The EAC excludes this study as it has an overlapping patient cohort with another included study.
Sporea I, Sirli R, Bota S, Popescu A, Sendroiu M, Jurchis A.	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.	Ultrasound in Medicine and Biology. 2012; 38(8):1310-6.	The EAC excludes this study as it has a mixed patient cohort.
Sporea I, Bota S, Peck-Radosavljevic M, Sirli R, Tanaka H, Iijima H, et al.	Acoustic Radiation Force Impulse Elastography for fibrosis evaluation in patients with chronic hepatitis C: An international multicenter study.	European Journal of Radiology. 2012; 81(12):4112-8.	The EAC includes this study. The sponsor also identified this study.
Sporea I, Bota S, Gradinaru-Tascau O, Sirli	Which are the cut-off values of 2D-Shear	European Journal of	The EAC excludes this study as it

Author(s)	Title	Publication	Decision
R, Popescu A, Jurchis A.	Wave Elastography (2D-SWE) liver stiffness measurements predicting different stages of liver fibrosis, considering Transient Elastography (TE) as the reference method ?	Radiology. 2014; 83(3):e118-e22.	does not use VTq.
Takahashi H, Ono N, Eguchi Y, Eguchi T, Kitajima Y, Kawaguchi Y, et al.	Evaluation of acoustic radiation force impulse elastography for fibrosis staging of chronic liver disease: A pilot study.	Liver International. 2010; 30(4):538-45.	The EAC excludes this study as it has an overlapping patient cohort with another included study.
Toshima T, Shirabe K, Takeishi K, Motomura T, Mano Y, Uchiyama H, et al.	New method for assessing liver fibrosis based on acoustic radiation force impulse: a special reference to the difference between right and left liver.	Journal of Gastroenterology. 2011; 46(5):705-11.	The EAC excludes this study as it has a mixed patient cohort.
Vermehren J, Polta A, Zimmermann O, Herrmann E, Poynard T, Hofmann WP, et al.	Comparison of acoustic radiation force impulse imaging with transient elastography for the detection of complications in patients with cirrhosis.	Liver International. 2012; 32(5):852-8.	The EAC excludes this study as it has a mixed patient cohort.
Yamada R, Hiramatsu N, Oze T, Morishita N, Harada N, Miyazaki M, et al.	Significance of liver stiffness measurement by acoustic radiation force impulse (ARFI) among hepatitis C patients.	Journal of Medical Virology. 2014; 86(2):241-7.	The EAC includes this study
Yap WW, Kirke R, Yoshida EM, Owen D, Harris AC.	Non-invasive assessment of liver fibrosis using ARFI with pathological correlation, a prospective study.	Annals of hepatology. 2013; 12(4):608-15.	The EAC excludes this study as it has a mixed patient cohort.
Ye XP, Ran HT, Cheng J, Zhu YF, Zhang DZ, Zhang P, et al.	Liver and spleen stiffness measured by acoustic radiation force impulse elastography for noninvasive assessment of liver fibrosis and esophageal varices in patients with chronic hepatitis B.	Journal of Ultrasound in Medicine. 2012; 31(8):1245-53.	The EAC includes this study.

Appendix 6: Search Strategy for Economic Evidence

Embase 1980 to 2014 Week 28, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; Searched on 14th July 2014

1	virtual touch tissue quantification.mp.	147
2	vtq.mp	66
3	acoustic radiation force impulse.mp.	992
4	acoustic radiation force impulse imaging.mp.	521
5	acoustic radiation force impulse elastography.mp.	158
6	ARFI elastography.mp.	201
7	transient elastography.mp	2479
8	ultrasound elastography.mp	882
9	TE.mp	2014
10	elasticity imaging techniques.mp. or Elasticity Imaging Techniques/	9032
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	10642
12	liver diseases.mp. or Liver Diseases/	170396
13	liver fibrosis.mp. or Liver Cirrhosis/	168425
14	Hepatitis/ or Hepatitis B, Chronic/ or Hepatitis, Viral, Human/ or Hepatitis B/ or Hepatitis C/ or Hepatitis C, Chronic/ or hepatitis.mp.	470226
15	12 or 13 or 14	697609
16	cost$.mp	1102202
17	economic$.mp	690492
18	16 or 17	1577913
19	11 and 15 and 18	173
20	limit 19 to english language	156
21	limit 20 to yr="2000 -Current"	156

22	limit 21 to humans	139
23	remove duplicates from 22	113

NHS EED and HTA databases (14 July 2013)

(acoustic radiation force impulse OR virtual touch tissue quantification OR elasticity imaging) IN NHSEED, HTA FROM 2000 TO 2014 (11)

ECONLIT (14 July 2013)

(Hepatitis/ OR Hepatitis B, Chronic/ OR Hepatitis, Viral, Human/ OR Hepatitis B/ OR Hepatitis C/ OR Hepatitis C, Chronic/ OR hepatitis.mp.) AND (acoustic radiation force impulse OR elasticity imaging OR virtual touch tissue quantification) AND (cost$ OR economic$) (0)