National Institute for Health and Care Excellence

External Assessment Centre correspondence

Virtual Touch Quantification to diagnose and monitor liver fibrosis

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
2 & 3	**Sponsor**	Multiple Questions –Teleconference notes & sponsor's written response included in Appendix 1.	No further action required.
2 & 3	**Email to Sponsor on 01/07/14:** Could you provide us with the reasons why the following three references (included in Appendix 2) were rejected	**Replies received on 02/07/14 and 09/07/14:** 18: P78 of the submission 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]. 16: It is a meeting abstract by the Romanian group. I took the view that there was probably overlap in the papers of which the name Sporea occurred. It may be that they are on performance pay. I included papers by these authors but not all of them. 1: The reason why I rejected reference 1 was at the time I couldn't get hold of it. I think this was because it was an electronic version prior to publication. 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.	No further action required.

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2	**Email to Sponsor on 02/07/14:** How does the 5.0 release (November 2013) improve robustness, as in how would a pre and post this release vary? Will it affect the results acquired to the extent that we should only be comparing papers using this particularly release?	**Reply received on 06/08/14:** The principle of the shear wave generation and estimation methods stays unchanged. Tuning of the shear wave generation and detection spatial configuration and signal processing pipelines have been done from version to version to increase the robustness of the estimates in the imaging field of view. These improvements in robustness do not affect the shear wave values. The effect is fewer “x.xx” values in more difficult patients, thus improving the success rate which was already quite a bit better than Fibroscan.	No further action required.
2 & 3	**Email to Expert Advisers (Hepatologists, Sonographers and Radiologists) on 03/07/14:** According to the current diagnostic algorithm for assessing fibrosis in chronic hepatitis B (HBV) and C (HCV), patients do not receive antiviral treatment until they reach stage F3 (METAVIR) for HBV and	**Reply from Paul Sidhu received 04/07/14:** This is a very clinical question. **Response from Philip Shorvon received 21/07/14:** This is a very clinical question which I cannot really answer **Response from David Sherman received 01/08/14:** The national and international guidelines for viral hepatitis are continually moving. For HCV, the prospect of shorter duration of treatment with new	No further action required.

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	stage F1-F2 (METAVIR) for HCV. Could you please clarify whether the claim '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' would be applicable in both HBV and HCV, or just HCV?	drugs available next year suggest that nearly all patients with HCV who do not have contraindications are likely to undergo treatment. Accurate non-invasive identification of fibrosis stage would be advantageous in this situation, however. With respect to HBV, decisions are made on inflammatory grade on biopsy as well as stage, in addition to LFTs, viral load and other factors. Some patients with F1 or F2 may be treated also. The other point is that Liver biopsy, the current gold standard, is not completely infallible, as we have learned in our work on ARFI / VTq over the past few years.	
All	**Email to Expert Advisers (Hepatologists, Sonographers and Radiologists) on 14/07/14:** 1. What is the overall prevalence of liver fibrosis among patients with chronic hepatitis B or C in England and Wales? What is its distribution for different stages of fibrosis (using	**Reply from Edmund Godfrey received 15/07/14:** Questions 1, 2, and 5 would be better addressed to a hepatologist, as a radiologist these questions lie outside my field of expertise. I have a research background in elastography and its accuracy in staging fibrosis rather than the management of patients with fibrosis. 3. There are no known adverse effects from diagnostic ultrasound. I am not aware of any and I do not foresee any problems with this technique. 4. In my practice, no shows are uncommon for liver biopsy appointments, a guesstimate would be 1 in 30-40 appointments.	No further action required.

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	Metavir score F1-F4)? 2. What is the expected annual disease progression for each stage of fibrosis? In other words, what proportion of patients diagnosed with fibrosis F1 or F2 is likely to progress to F3 or F4 annually? Likewise, what's the proportion of patients diagnosed with F3 fibrosis expected to progress to F4 fibrosis annually? 3. From our searches, we have identified no reported adverse events with this technology. Are there any adverse events which you are aware of, or are there any which you could see potentially occurring?	**Reply from Priya Narayanan received 16/07/14:** Many of these questions would be best answered by a hepatologist. With regards to adverse events, I have had none and do not know of adverse effects quoted in the literature. **Reply from Philip Shorvon received 21/07/14:** Your questions are very pertinent and many require a very detailed knowledge of the literature of the clinical aspects of Hep B and Hep C infections which I do not have. I am a radiologist so more in tune with the literature surround the test rather than epidemiology of the diseases. The literature certainly suggests that the accuracy of TE and ARFI VTq are similar (if not in favour of ARFI) and therefore the arguments for its inclusion in clinical pathways is also similar. Conversely if you are going to look at whether elastography should be in the hepatitis pathways (as in the current NICE guidance for Hep B) this will probably aslo apply to TE 1. I do not have data on this. 2. Again I do not have data on this. 3. I know of no adverse effects and would not expect one. It uses	

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	4. Would you be able to give a rough idea of the proportion of 'no shows' for liver biopsy appointments? 5. Would you consider clinical studies conducted in other European countries (such as Romania and Germany) as being applicable to the UK population? What about studies conducted within Asia (e.g. China, Taiwan and Japan)? Are there significant differences between the results acquired using VTq in different ethnic groups?	ultrasound which are decades of use has been shown to be safe. It does use a high energy pulse but puts a cooling time between reading. 4. This will be variable according to where your service is. We have a large population of first and second generation immigrants, in whom half the population do not have English as their first language, who are on the move a lot and who go back to their countries of origin very often. As a consequence we do get DNA's- around 10%. In a less diverse population I would expect less than 5% as the biopsy is a major event in their lives which many find very daunting and by the time they agree they want to get it over with as quickly as possible 5. I do not know any data comparing ethnic groups. One issue is the prevalence of obesity- the technique has more failures with obese subjects and probably more variable results. In some Asian countries obesity is much less prevalent. Furthermore there are different genotypes but I don't know of studies comparing the accuracy in different genotypes. **Reply from Paul Sidhu received 24/07/14:** 1. I cannot answer this. 2. I cannot answer this. 3. There are no adverse effects with this technology in the liver –	

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		concern about the energy input into smaller vulnerable structures e.g. retina have been raised, without evidence of damage, and should not be used on the developing fetus. 4. In ultrasound 10-15%. 5. German and Romanian studies may not be applicable to the UK as our Hep b/C population is worldwide; we need to have local UK studies Same with China/Japan =- these patients are very different particularly body habitus!! I am not sure about any differences between ethnic groups – maybe a good study! **Reply from David Sherman received 01/08/14:** 1. I have looked in the NICE guidelines and elsewhere for this data and cannot find reliable UK data. I discovered this paper which represents international figures from Hep B trials from several centres, which is of some use, however. Given the variability between regions and ethnic make up, it may be difficult to get really accurate data. I would estimate that 20 – 25% of both HCV and HBV patients at our centre are F3 or F4, for example. We have data on about 100 patients with simultaneous Biopsy and ARFI / VTq, and I will try and get this for you. A more detailed search	

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		may be needed. 2. Cannot give a short answer on this one. Many factors influence disease progression. For HCV, it is said that the progression from F0 at infection to F4 cirrhosis takes 20 – 30 years, but not all do progress at this rate. For HBV, variability is greater depending upon host factors, progression through virological life cycles, age of infection etc. As such, you are looking at shorter periods of 5 years to longer possibilities of 50 or more ! But variation is enormous. You may need your resources to do a formal literature review on these topics, however. 3. Not really ! I am not aware of any direct adverse effects. 4. In our Institution I would estimate 5% or less, but can check with my colleague if accurate data needed. 5. An interesting question. I think that the answer is “Yes” provided the samples are corrected for age, BMI, technique, liver disease aetiology and technical factors. I doubt (but do not know) that race / ethnic origin itself is an independent predictor of liver stiffness, nor is there	

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		any evidence of the same!	
All	**Email to Expert Advisers (Hepatologists) on 16/07/14:** Are there any groups of patients for whom VTq is not a suitable technique?	**Reply from David Sherman received 01/08/14:** Not really, although we do not do sick patients in ITU because the machine is not portable, and ascites and other factors would reduce the success rate. The other area that really should be considered is CHILDREN – there is a great need for accurate non-invasive diagnosis in this group, without the need for biopsy.	No further action required.
4	**Email to Sponsor on 16/07/14:** In Table C1 (Prisma diagram) on page 87 of the submission, it is indicated that 11 potentially relevant publications were found. Of these, 4 + 1(CEP report) were included for review. Is there any chance you could provide us with the references for the 7 excluded studies?	**Reply received on 17/07/14:** References provided (see appendix 3).	No further action required.

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2	**Email to Sponsor on 21/07/14:** In section 4 (regulatory information), you state that the product has been CE marked since 2008. The attached declarations of conformity were dated 2012. Would it be possible to see the ones from 2008 as well?	**Reply received on 22/07/14:** Attached 2008 declaration of conformity, as requested (Appendix 4).	No further action required.
2/3	**Email to Expert Advisers (Hepatologists, Sonographers and Radiologists) on 25/07/14:** Do you consider the current clinical pathway, and the potential new clinical pathway including VTq presented by the sponsor for hepatitis B and hepatitis C to be appropriate? Are there any changes you would make or deviations to	**Reply from David Sherman received 01/08/14:** I have looked at both the TE bases and VTq / ARFI based pathways. I assume that these are based upon the published evidence as outlined. With respect to Hep C, I think that from personal experience very few patients are now biopsied and, with the advent of even more effective drug therapy this need will reduce. The pathways suggest that for TE it is important to biopsy those with intermediate liver stiffness values, due to the date suggesting reduced accuracy for prediction of Metavir stage. In practice, biopsies may be done more in those not proceeding to treatment, and in those who treatment has failed to achieve an SVR.	No further action required.

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	current NHS practice? (The four clinical pathways are in the document attached?)	For VTq in Hep C, the assumption is that the accuracy is less at the lower end of the range, but the evidence in this area needs review, I think. My feeling is that the need for biopsy will continue to drop in this group. The situation is different for Hep B, where biopsy is needed for groups with intermediate or lower liver stiffness. Is the data there to make a distinction between TE and ARFI ? – I think that careful re-appraisal of the studies may be needed. In the case of Hep B, one of the major determinates of the need for biopsy is the worry about missing significant necro-inflammation in the liver which is not detected by stiffness measurements (see recent EASL / AASLD guidelines), so ALT levels, E antigen status and particularly quantitative Hepatitis B DNA levels (intermediate values between 2,000 and 20,000 IU/ml, for example) are also taken into account. These can be very important factors contributing to a decision on treatment. I think therefore that these specific HBV DNA levels and “high / low risk” status should be added to the algorithm for VTq in Hep B, but the views of other experts in this area would be of interest.	

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All	**Email to Sponsor on 25/07/14:** Could you confirm whether n/a means 'not available' at all points it is present in the submission, or whether any are in fact 'not applicable'.	**Reply received on 29/07/14:** In part A and B as discussed earlier I have used n/a as not available while in part C table 3c I have used n/a as not applicable.	No further action required.

Appendix 1

Questions posed to sponsor in introductory tele-conference (between KiTEC, NICE and sponsor) held on the 18th of June, 2014.

Present in the Teleconference:

NICE – Bernice Dillon, Jo Higgins
Sponsor – Bernadette Leonard, Anthony Stevens (main contacts at the sponsor)
KiTEC – Murali Kartha, Tiago Rua, Anita Patel, Elizabeth Morris, Anastasia Chalkidou, Jennifer Summers, Neil Lewis

Please find KiTEC's questions in black, replies provided by the sponsor at the teleconference (minuted by KiTEC) in red and the sponsor's written replies (provided on 28.06.14) in blue.

1. Page 24, Section 3.6
   According to the current diagnostic algorithm for assessing fibrosis in chronic hepatitis B (HBV) and C (HCV), patients do not receive antiviral treatment until they reach stage F3 (METAVIR) for HBV and stage F1-F2 (METAVIR) for HCV. Could you please clarify whether your claim is that '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' is applicable in both HBV and HCV, or just HCV?

   It has been suggested this question is put to the expert advisers. Sponsor thought it was a moving picture at which stage you start the antivirals, possibly dependent upon individual clinicians. Comment is related to patients getting a diagnosis sooner rather than later.

   CLINICAL QUESTION but earlier treatment may be unwarranted as fibrosis evolves so slowly as not to be an issue while the cost of antiviral treatments is expensive and have side effects.

2. Page 36, Figure B1
   The flowchart of the study identification includes a subsection identified as Siemens Clinical Abstracts. Could you please provide further information regarding the process for obtaining these abstracts, whether or not they exist on an accessible database, and what the date 8/2013 corresponds to?

Siemens clinical abstracts is a collection of the abstracts from 8/2013 on the ARFI/VTq technology for advertising purposes. Anthony to forward to KiTEC

The date was the date of the publication. These are abstracts collected by Siemens illustrating the use of the technology and that we would expect to be a fair appraisal of publications.

3. Page 47, Table B6, Reference 44
   In the row on primary outcomes, results on correlation are not clear (CHECK is written, rather than YES/NO). Could this please be clarified?

   Check should be replaced by No. Paper didn't correlate ARFI or VTq with liver biopsy.

   They did not correlate ARFI vs LB.

4. Page 56, Section 7.5
   According to the information provided in this section, data on study details, study participants, index test, reference test and comparators were extracted. Could you please provide more details regarding the characterization 'n/a' for the items 'minimise bias', 'outcome minimise bias', and 'follow up' for all of the studies? Additionally, could you provide more details for the identified confounding factors for studies 2, 45 and 55 (answered as Yes in the relevant section of table B8)?

   The follow up question relates to one off studies where there was no repeated follow up of patients.
   Bias and confounding factors have been discussed in 7.4.2
   Correlation is expected to be better for patients with F3 and F4 scores than lower scores.

   bias - The population HvB, HvC and the severity of fibrosis. A number of the studies probably exhibit spectrum bias as the patients studied may not be representative of the clinical patients. In other words heavily weighted to severe fibrosis and cirrhosis as patients suspected of these conditions are most likely to be biopsied. In some studies volunteers were used with the assumption that they had no fibrosis leading with the potential for verification bias.
   follow up - There was no follow up of patients reported
   confounding factors - In the individual papers there are no confounding factors as the patient groups for all measurements are identical.

5. Pages 64-74, Table B9
Could you please provide a description of each item included in the table and how the terms 'not applicable' (n/a) and 'not relevant' were decided? For example in reference 61 and 48 you provide the following:

Reference	61	48
Study title	Performance of a new elastographic method (VTQ technology) compared to unidimensional transient elastography in the noninvasive assessment of chronic hepatitis C. Preliminary results	How efficient is acoustic radiation force impulse elastography for the evaluation of liver stiffness?
VTQ value	r=0.717	r = 0.646
VTQ 95% CI	Not relevant	n/a
VTQ type	n/a	Spearman

n/a has been used as not available rather than not applicable. Most papers don't provide all of the fields requested.

Correlation coefficient rho [r]. There are no confidence intervals for this measurement.
(n/a) = Not available

6. Page 75, Section 7.7.2
In the sentence "Adverse events associated with liver biopsy are well described (ref)", reference is missing. Could this be provided?

Anthony to provide reference to KiTEC

Bravo AA, Sheth SG, Chopra S (2001) Liver biopsy. N Engl J Med 344:495–500

7. Page 79, Table B11
Could you justify the inclusion of reference xi in table B11 results? This study is not one of the studies considered (table B3) or included (table B8) in the review.

This paper is for discussion mostly. Related to the comment about antiviral therapy = possibly relevant in economic analysis?

Reference xi 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.

8. Page 82, Section 7.9.1
   Could you confirm exactly which patient populations cannot use the VTq software? Page 82 indicates approximately 97% of patients are suitable for investigation using VTQ. Could you elaborate on the patient characteristics of the 3% who may not be suitable?

   This figure comes from the literature, so will check papers to identify their excluded patients. In general, VTq is not sensitive to the BMI of the patients. There may be problems with morbidly obese patients, in whom you are unlikely to be able to get a good liver image anyway. Also should be noted that the mix of patients in the papers varies.

   Inability to get ten repeat measurements, or (quality criteria IQR (the difference between the 75th and the 25th percentile – the median), 30% and success rate (SR) >=60%).

9. Page 118, Section '10.1.3'
   According to the initial statement the dates of the searches were: 'The date span of the search: 2009 to date'. On the individual database search description, the date span is noted as MEDLINE (PubMed 2000– May 2014 Week 3) and EMBASE (searched 20/05/2014). Could you please clarify the correct chronological limits of the systematic review search? Could you also provide a justification for the use of the specific chronological limits?

   The first ARFI papers were published in 2009

   The first papers on ARFI were published in 2009 and therefore there was no need to place date limits on the search.

10. Page 118-119, Section '10.1.3'
    In the search strategy (Medline), the search terms combined using Boolean operators are missing. Can this be made available?
    In the search strategy (Embase), for #7("1 and 5 and hepatitis") & #8 ("1 and 5 and hepatitis and fibrosis [Title/Abstract]"), shouldn't it be 6 instead of 5? YES
    The search strategy for CDSR, DARE & HTA databases are missing. Can this be made available?

Anthony to forward these to KiTEC
He was not sure on the search strategy question.

(((arfi[Title/Abstract]) OR vtq[Title/Abstract])) AND hepatitis
CDSR: ARFI
DARE: Elastography and liver and fibrosis
HTA: Elastography and liver and fibrosis (HTA in progress and submitted)

11. Page 118-119, Section '10.1.3'
Could you please clarify whether the use of the terms VTq and VTQ correspond to the abbreviations given in page 9 and whether the full terms Virtual Touch™ Tissue Quantification (VTq) and Acoustic Radiation Force Impulse (VTQ) were actually used in your search strategy?

Acoustic radiation force impulse should have been within the MESH terms for ARFI so they should both have been included within the search performed. In the search stratgey, the first line should be ARFI rather than VTQ.

YES – in the Embase search there is an error and the first search term should read 1.ARFI [Title/Abstract] or VTq[Title/Abstract] or Virtual Touch Quantification[Title/Abstract] 563. See below references

12. References
Could you please clarify why some of the references have had their titles changed so that the word 'ARFI' (in the original paper) is replaced with 'VTQ' (in the reference list)? Examples include references 18, 21, 22 and 31.

A 'search and replace' mistake

Unfortunately the perils of using find and replace. The term VTQ (caps) should be replaced (search and replace) by ARFI in the document.

13. General
Do all the submitted studies use the same version of the VTq software? If different versions of the software have been used, what are the fundamental differences between them?

Bernadette is going to contact the engineers about this question to see about modifications in VTq. There is nothing evident in the papers.

Over time, the depth it was possible to measure the shear waves has been improved (through software updates to the ultrasound operating system). It is thought that there were no other alterations.
Further information will be provided.
Further studies – people have started using the technique and moved on from the studies which otherwise would have been completed.

The software used will depend on the date of the study. No paper mentions the software version. The major change has been the increase in depth which has allowed measurements to be routinely made from 2-3 cm below the surface of the liver. The majority of papers comment on the depth that the sample was taken but a few erroneously measure this depth from the probe surface. The accuracy of measurements reported in papers where the depth was 2cm or greater is higher than from those where depth is not described or measurements are made superficially.
1.0 Initial Release: 2009 with 4C1 and 4V1 abdominal transducers
2.0 Release: June 2010. Increased depth limit from 5.5 cm to 8.0 cm
3.0 Release: September 2011. No change
3.1 Release: October 2012. Added VTq to 6C1 HD abdominal transducer
4.0 Release: October 2012. No change
5.0 Release: November 2013. Improvements in shear wave signal processing to improve robustness

Appendix 2

1	R	Optimal linear combination of ARFI, transient elastography and APRI for the assessment of fibrosis in chronic hepatitis B	Liu Y., Dong C.f., Yang G., Liu J., Yao S., Li H.y., Yuan J., Li S., Le X., Lin Y., Zeng W., Lin H., Zhang X., Chen X.	Liver International (2014). Date of Publication: 2014
16	R	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?	Bota S., Sporea I., Sirli R., Popescu A., Danila M., Jurchis A., Gradinaru-Tascau O.	Ultraschall in der Medizin, Supplement (2013) 34 SUPPL. 1. Date of Publication: September 2013
18	R	Meta-analysis: ARFI elastography versus transient elastography for the evaluation of liver fibrosis	Bota S., Herkner H., Sporea I., Salzl P., Sirli R., Neghina A.M., Peck-Radosavljevic M.	Liver International (2013) 33:8 (1138-1147). Date of Publication: September 2013

Appendix 3

Title	Author Names	Source
Cost and time savings from a rapid access model of care using transient elastography to screen and triage patients with chronic Hepatitis C infection	Whitty J.A., Tallis C., Nguyen K.-H., Scuffham P.A., Crosland P., Hewson K., Pai Mangalore R., Black M., Holtmann G.	Journal of Medical Economics (2014) 17:2 (159-165). Date of Publication: February 2014
Ultrasound elastography for fibrosis surveillance is cost effective in patients with chronic hepatitis c virus in the UK	Canavan C., Eisenburg J., Meng L., Corey K., Hur C.	Digestive Diseases and Sciences (2013) 58:9 (2691-2704). Date of Publication: September 2013
A health technology assessment of transient elastography in adult liver disease	Steadman R., Myers R.P., Leggett L., Lorenzetti D., Noseworthy T., Rose S., Sutherland L., Clement F.	Canadian Journal of Gastroenterology (2013) 27:3 (149-158). Date of Publication: March 2013
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	Stevenson M., Lloyd-Jones M., Morgan M.Y., Wong R.	Health Technology Assessment (2012) 16:4. Date of Publication: February 2012
Diagnosis and treatment of chronic hepatitis B and D. Hungarian national consensus guideline **(Rejected)**	Horvath G., Hunyady B., Gervain J., Lengyel G., Makara M., Par A., Szalay F., Telegdy L., Tornai I.	Orvosi Hetilap (2014) 155:SUPPL. 2 (25-35). Date of Publication: 2014
Cost effectiveness of rapid access to assessment and treatment model of care: Targeted hepatitis C clinics **(Rejected)**	Mangalore R.P., Tallis C., Stuart K.A., Black M., Whitty J., Hewson K., Holtmann G.	Journal of Gastroenterology and Hepatology (2013) 28 SUPPL. 2 (175). Date of Publication: October 2013
Noninvasive markers of fibrosis: Key concepts for improving accuracy in daily clinical practice **(Rejected)**	Duarte-Rojo A., Altamirano J.T., Feld J.J.	Annals of Hepatology (2012) 11:4 (426-439). Date of Publication: 2012
Evaluation of the costs of Transient Elastography (FibroScan ((registered trademark))) in the diagnosis of liver fibrosis in HIV patients with hepatitis C virus **(Rejected)**	Garcia-Jurado L., Oyaguez I., Casado M.A., Tural C., Gonzalez-Garcia J., Ortega E., Pineda J.A.	Enfermedades Infecciosas y Microbiologia Clinica (2012) 30:6 (294-299). Date of Publication: June-July 2012
Utilization of liver biopsy in chronic hepatitis c infection: The experience of a Victorian tertiary hospital with a Fibroscan(registered trademark) service **(Rejected)**	Majumdar A., Roberts S., Mclean C., Wijayarante S., Kemp W.	Journal of Gastroenterology and Hepatology (2012) 27 SUPPL. 4 (87-88). Date of Publication: October 2012
Transient elastography (Fibroscan) in chronic hepatitis B infection: Reduce number of biopsies and save money **(Rejected)**	Guirgis M., Manoharan S., Scott D.R., Kwok R., Lee A.U., Connor S.J., Levy M.T.	Journal of Gastroenterology and Hepatology (2009) 24 SUPPL. 2 (A308). Date of Publication: October 2009
Defining cirrhosis with fibroscan for entry to hepatocellular carcinoma surveillance in chronic hepatitis C: A UK cost effectiveness analysis **(Rejected)**	Canavan C., Corey K., Hur C.	Gut (2013) 62 SUPPL. 1 (A35). Date of Publication: June 2013

Appendix 4

SIEMENS

EC DECLARATION OF CONFORMITY

according to Annex II.3 to Council Directive 93/42/EEC of June 14, 1993

Manufacturer	Siemens Medical Solutions USA, Inc. 1230 Shorebird Way Mountain View, CA 94043 USA
Facility	Siemens Medical Solùtions USA, Inc. 1230 Shorebird Way, Mountain View, CA 94043 USA
EC Representative	Siemens AG Medical Solutions Henkestrasse 127, 91052 Erlangen, Germany
Medical Device	ACUSON S2000™ ultrasound system
Product identification	See attached table
Classification	Class IIa (according to Annex IX to Council Directive 93/42/EEC, Rule 10)
Date of First CE Mark	February 22, 2008

We declare the compliance of the above medical device with the requirements of the Council Directive 93/42/EEC of June 14, 1993. Any modification of the medical device not authorized by us will invalidate this declaration.

The conformity of the full quality assurance system is certified by:

TÜV PRODUCT SERVICE GmbH
Ridlerstrasse 65
DE-80339 Munich
Germany

The identification number of the notified body for implementation of the procedure set out in Annex II to the above Directive is 0123.

This Declaration applies also to all accessories.

Place and date	Mountain View, March 29, 2008
Name	Lars Becker (Head of Quality Management))
Signature	L. M

For conditions of guarantee and liability please refer to our General Conditions of Sale.

Page 1 of 2

EC DECLARATION OF CONFORMITY

EC DECLARATION OF CONFORMITY

Product identification

System	S2000	Part No. 10041461
Transducer	14L5	Part No. 10041221
Transducer	9L4	Part No. 10041588
Transducer	4V1	Part No. 10041584
Transducer	7CF2	Part No. 10041222
Transducer	9EVF4	Part No. 10041223
Transducer	6C2	Part No. 10041591
Transducer	4C1	Part No. 10041590
Transducer	4P1	Part No. 10041224
Transducer	CW2	Part No. 10041655
Transducer	CW5	Part No. 10041656
Transducer	V5Ms	Part No. 10041657
Transducer	EC9-4	Part No. 10041225
Transducer	10V4	Part No. 10041585

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