National Institute for Health and Clinical Excellence

# NATIONAL INSTITUTE FOR HEALTH AND CLINCIAL EXCELLENCE

## Diagnostics Assessment Programme

## SonoVue (sulphur hexafluoride microbubbles) - contrast agent for contrast enhanced ultrasound in liver imaging

## Final scope

October 2011

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# 1 Introduction

The Medical Technologies Advisory Committee identified SonoVue as potentially suitable for evaluation by the Diagnostics Assessment Programme (DAP) on the basis of a briefing note. SonoVue is manufactured by Bracco UK Limited.The scope outlines the approach for assessing the clinical and cost effectiveness of SonoVue for liver imaging.

The scope has been compiled using a variety of sources, including the briefing note, a request for information from the manufacturer and expert opinion including feedback from attendees at the scoping workshop held on 23 August 2011 and input from assessment subgroup members. NICE has not carried out an independent evaluation of this information. Assumptions made in the scope will be verified in the assessment.

# 2 Description of the technologies

## 2.1 The notified technology

SonoVue (Bracco UK Ltd) is a contrast agent involving sulphur hexafluoride microbubbles for contrast enhanced ultrasound (CEUS) imaging in adults.

SonoVue consists of a kit containing a vial of sulphur hexafluoride gas and phospholipid powder, a pre-filled syringe of solvent (sodium chloride solution) and a transfer and ventilation system (mini spike). The saline is introduced into the vial by the mini spike delivery system and once reconstituted, millions of tiny microbubbles are formed. These microbubbles are the contrast agent which is injected into a peripheral vein at the ante cubital fossa. An ultrasound probe is placed on the abdomen and the ultrasound waves cause the microbubbles to resonate so that a signal is picked up by a transducer and an image is formed on a screen. SonoVue can be used with the majority of modern ultrasound equipment, with the exception of a few portable machines.

As this contrast agent is a pure blood pool agent it remains within the patient's blood vessels and, depending on the type of lesion, it shows a pattern of uptake identical to that of CT or MRI contrast agents. Generally for benign lesions the lesion will remain bright or isoechoic with the rest of the liver, for malignant lesions the area will wash out and leave a black hole.

The contrast agent is broken down by the body after a few minutes and the sulphur hexafluoride gas is exhaled through the lungs and the phospholipid component of the microbubble shell is metabolised (re-entering the endogenous phospholipid metabolic pathway).

SonoVue is a second generation contrast agent. These agents have a flexible shell which allows continuous imaging (at a low mechanical index) without early destruction of the microbubble. First generation agents have now been superseded by second generation agents and are no longer available in Europe.

### 2.1.1 Therapeutic indications

The following section is taken from the Summary of Product Characteristics for SonoVue:

*This medicinal product is for diagnostic use only.*

*SonoVue is for use with ultrasound imaging to enhance the echogenicity of the blood, which results in an improved signal to noise ratio.*

*SonoVue should only be used in patients where study without contrast enhancement is inconclusive.*

*Echocardiography: SonoVue is a transpulmonary echocardiographic contrast agent for use in patients with suspected or established cardiovascular disease to provide opacification of cardiac chambers and enhance left ventricular endocardial border delineation.*

*Doppler of macrovasculature: SonoVue increases the accuracy in detection or exclusion of abnormalities in cerebral arteries and extracranial carotid or peripheral arteries by improving the Doppler signal to noise ratio. SonoVue increases the quality of the Doppler flow image and the duration of clinically-useful signal enhancement in portal vein assessment.*

*Doppler of microvasculature: SonoVue improves display of the vascularity of liver and breast lesions during Doppler sonography, leading to more specific lesion characterisation.*

The focus of the evaluation is on CEUS in liver imaging only. In particular, the characterisation and detection of focal liver lesions (FLLs) is seen as the most important application of CEUS within liver imaging. In addition, there may be significant overlap between the characterisation and detection of FLLs and the role of CEUS in monitoring treatment for FLLs. Therefore, if data are available, the role of CEUS in monitoring treatment should also be considered in the evaluation. With regards to the role of CEUS in monitoring treatment for FLLs, initial searches have identified data on the use of CEUS in monitoring the results of percutaneous treatment and antiangiogenic therapy (note – NICE does not recommend the use of Sorafenib for the treatment of advanced hepatocellular carcinoma (NICE Technology Appraisal 189)).

## 2.2 Potential alternative technologies

Reference to a range of contrast agents for use in contrast enhanced ultrasound can be found in the literature. Potential alternative technologies that have received a central marketing authorisation by the European Commission include Luminity (Lantheus Medical Imaging) and Optison (GE Healthcare). It is important to note that these technologies are indicated for use in echocardiography only. Therefore, as the focus of the evaluation is liver imaging, Luminity and Optison have not been included in the scope.

# 3 Target indications

## 3.1 Focal liver lesions (FLLs)

A focal lesion in the liver refers to any tissue abnormality occurring in one specific area of the liver. FLLs can be classified into two main categories, namely, benign or malignant.

Benign FLLs include haemangioma, focal nodular hyperplasia, focal fatty sparing and adenoma.

Malignant FLLs include primary cancer of the liver, known as hepatocellular carcinoma, and secondary cancers of the liver (metastases) resulting from primary cancers occurring elsewhere in the body (for example colorectal cancer, breast cancer, lung cancer and pancreatic cancer).

Once a lesion has been detected in an individual the foremost concern is to differentiate between benign and malignant lesions. This distinction determines the individual's prognosis and the subsequent treatment strategy. Benign liver lesions, due to their asymptomatic nature, often do not require any treatment. In such cases, it is common for the individual to be monitored and the lesion rescanned in 6 - 12 months. Once a malignant lesion is identified it is important to distinguish between primary and secondary cancers as this is likely to impact how the individual is managed. Malignant lesions may be treated by a range of interventions including chemotherapy, liver resection (surgery), and radiofrequency ablation.

Expert opinion suggests that as many as 70 – 75% of FLLs assessed in the NHS may be benign. Approximately 3,200 people in the UK are diagnosed with primary liver cancer (approximately 85% have hepatocellular carcinoma) while approximately 90,000 people are diagnosed with secondary liver cancer every year.

The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) produced guidelines and good clinical practice recommendations for CEUS in 2004. The latest version of the guidelines was published in 2008. The 2008 version of the EFSUMB guidelines are currently being updated and may be available before the scope is finalised for this evaluation. The 2008 EFSUMB guidelines note the use of CEUS in focal liver disease as the single most important application of this technique after echocardiography. The 2008 EFSUMB guidelines include sections on the detection and characterisation of FLLs and, monitoring of local ablative treatment for the liver.

## 3.2 Other uses of SonoVue

Given the range of areas that may be assessed within the marketing authorisation of SonoVue, the identification and potential inclusion of other target uses (including echocardiography, abdominal trauma and CEUS-guided therapy) were discussed at the scoping workshop. Attendees, including clinical experts, felt that NICE guidance would be most valuable

within liver imaging, where practice varies nationally and sufficient data are available to evaluate the use of SonoVue in that setting.

### 3.3 CEUS of the liver

The liver is supplied by two blood vessels, the hepatic artery and the portal vein, and three overlapping vascular phases of the liver can therefore be visualised using CEUS. While individual patient haemodynamics will influence the onset of the three vascular phases the approximate time to visualisation after injecting the contrast agent into a peripheral vein can be seen in table 1.

**Table 1 – Visualisation of liver vascular phases**

| | Approximate time to visualisation of vascular phase post-injection of contrast agent (seconds) | |
|---|---|---|
| Phase | Start | End |
| Arterial (hepatic artery) | 10 - 20 | 25 – 35 |
| Portal-venous | 30 - 45 | 120 |
| Late | 120 < | 240 – 360 (bubble disappearance) |

Information on the extent and pattern of vascularity can be ascertained during the arterial phase, and this phase is therefore used mainly for *characterising* focal liver lesions. Information about the washout of the contrast agent from the lesion when compared to normal liver tissue can be determined during the portal and late phases, so these phases are used mainly for the *detection* of malignancies.

CEUS allows imaging of blood flow at the tissue perfusion level and therefore improves on the imaging capability of unenhanced ultrasound (B-Mode or Colour Doppler, with which the ability to detect blood flow at the perfusion level is limited). CEUS may also be used as an alternative to Computed Tomography (CT) with contrast and Magnetic Resonance Imaging (MRI) with contrast. The 2008 EFSUMB guidelines note that in some cases CEUS has greater accuracy than CT with contrast.

# *4 Diagnostic and care pathways*

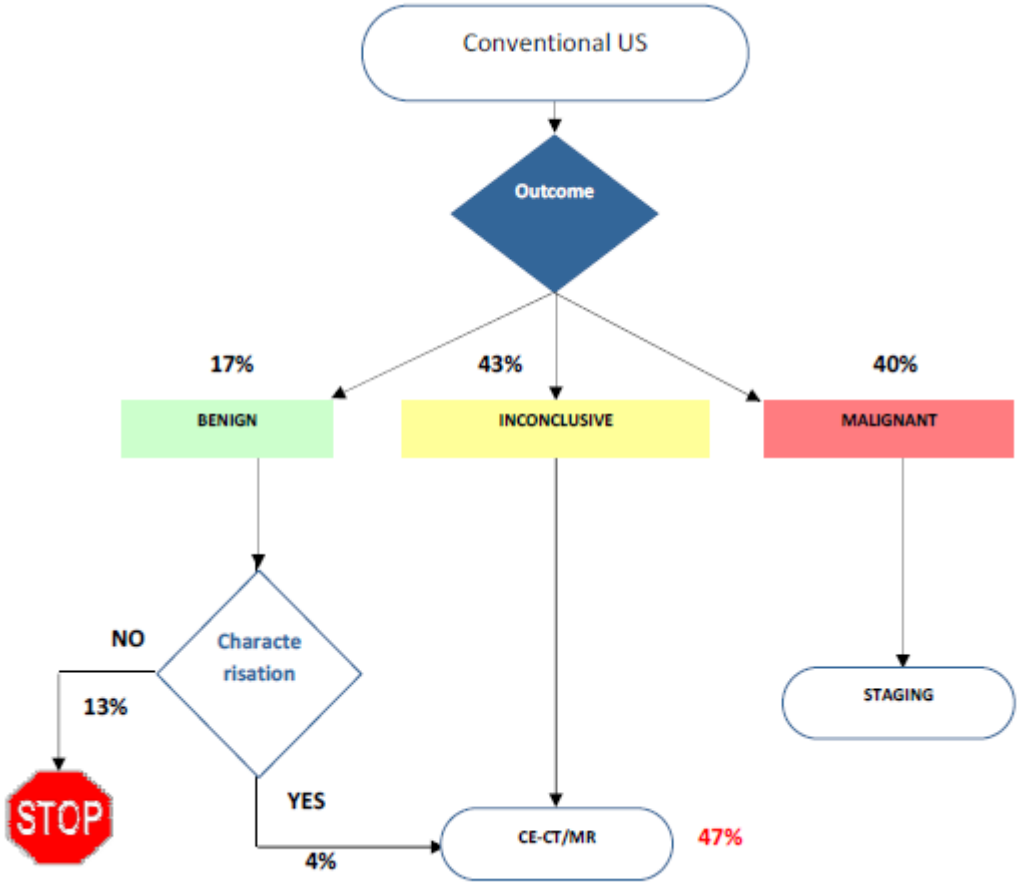
## 4.1 Diagnostic pathway

### 4.1.1 Current practice for liver imaging

An initial scan using unenhanced ultrasound (B-Mode or Colour Doppler) is usually conducted in individuals with suspected focal liver disease. This is due to the relative safety and availability of this modality, and its low cost. Inconclusive results require further investigation. Further investigation using imaging techniques usually involves CT with contrast agent and/or MRI with contrast agent. In some cases it is possible that individuals may start with an initial CT/MRI with contrast scan and may then go on to receive an ultrasound scan (with or without contrast). An example of a typical imaging algorithm used in current practice can be found in diagram 1 (a range of diagnostic strategies may be used in the NHS in England and are discussed further in section 6.1.2).

The 2008 EFSUMB guidelines and other guidelines (e.g. European Association for the Study of the Liver (EASL) guidelines discussed in section 4.2) can be used to understand the diagnostic pathway used for the characterisation and detection of FLLs in the NHS in England.

**Diagram 1 – Example of an algorithm for liver imaging – current practice without CEUS (supplied by the manufacturer – Bracco)**



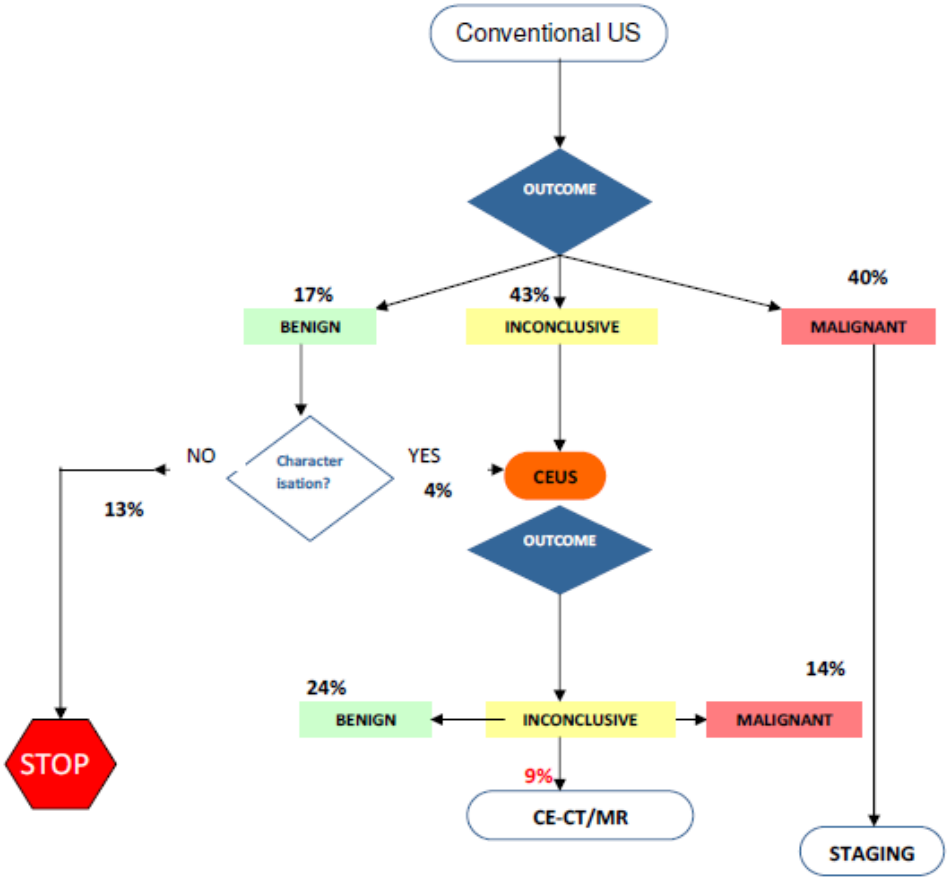

In this example, lesions are characterised and divided into three groups after the initial ultrasound scan. Lesions clearly characterised as malignant (40%) go on to be staged (Specialist Committee Members suggest that a biopsy is unlikely to be performed on the basis of an unenhanced [conventional] ultrasound scan alone. In reality, further imaging and other tests (for example, tests for tumour biomarkers) are likely to be performed before deciding to biopsy the liver lesion/s). The majority of benign lesions are clearly characterised during the initial ultrasound scan and do not require further testing (13%). A small number of benign lesions (4%) may require further testing to confirm the diagnosis. These lesions and the inconclusive results (43%) undergo further testing to aid characterisation of the lesion. Thus, 47% of lesions go on to be characterised by either CT or MRI with contrast. This will require the individual to make another outpatient appointment – in some cases, several months may pass between the initial ultrasound scan and subsequent imaging. Further FLLs may be detected during the contrast enhanced CT/MRI scan that did not appear on the baseline ultrasound scan. These FLLs can be characterised at this stage as described in section 3.3. Certain malignant lesions may be diagnosed without the need for a biopsy

(e.g. American Association for the Study of Liver Diseases (AASLD) guidelines (discussed in section 4.2) state that 'Detection of a hepatic mass within a cirrhotic liver is highly suspicious of HCC. If alpha-fetoprotein is greater than 200 ng/mL and the radiological appearance of the mass is suggestive of HCC (large and/or mutifocal disease with arterial hypervascularity), the likelihood that the lesion is HCC is high and biopsy is not essential.').

#### 4.1.2 CEUS in current practice for liver imaging (supplied by the manufacturer – Bracco)

It is suggested that CEUS be used in conjunction with current practice and as the next imaging modality following the initial ultrasound scan as described in diagram 2. Although seen as 2 separate stages in the diagram, in reality, a CEUS scan may be conducted in the same appointment as the initial ultrasound scan.

**Diagram 2 – Example of an algorithm for liver imaging – proposed practice with CEUS (supplied by the manufacturer – Bracco)**



In this example and following on from diagram 1, the 47% of lesions that require further testing after the initial ultrasound scan go on to receive CEUS. Further FLLs may be detected during the CEUS scan that did not appear on the baseline ultrasound scan. These FLLs can be characterised at this stage as described in 3.3. As a result, fewer lesions (9%) require imaging using the more expensive CT/MRI with contrast modalities.

#### 4.1.3 Reference standard

Ultimately, an individual's true diagnosis may only be uncovered using histological confirmation (via biopsy or surgical excision). However, not all patients will have such specimens, especially if the lesion is thought to be benign. Therefore, the reference standard seen in the literature is often made up of a combination of CT with contrast, MRI with contrast, histological confirmation and follow-up.

### 4.2 Care pathway

The care pathways for this assessment may be ascertained from clinical guidelines. Guidelines that may be useful for this evaluation include:

- European Association for the Study of the Liver (EASL) guidelines for the' Management of hepatocellular carcinoma'(published in the American Association for the Study of Liver Diseases (AASLD) guidelines for the' Management of hepatocellular carcinoma (2005)'

- UK Guidelines for the management of suspected hepatocellular carcinoma (HCC) in adults

Individuals with malignant lesions may be managed by a range of interventions including chemotherapy, liver resection (surgery), local ablation therapy, liver transplant and palliative care. Expert opinion suggests that practice within the NHS may vary significantly across regions based on clinician preference. Therefore, expert opinion may be needed to better understand the typical care pathway for managing FLLs in the NHS in England.

# 5 Scope of the evaluation

## 5.1 Populations

Adults with suspected focal liver disease.

## 5.2 Interventions

SonoVue.

For the characterisation and detection of FLLs. The role of SonoVue in monitoring treatment of FLLs should also be included if data are available.

## 5.3 Comparators

Current practice – a combination of unenhanced ultrasound, CT/MRI with contrast, histology and follow-up.

CEUS can be used either as a replacement for CT/MRI with contrast, or as a triage step to reduce the use of CT/MRI with contrast.

## 5.4 Healthcare setting

Secondary and tertiary care.

## 5.5 Health Outcomes

The outcomes of interest are the morbidity and mortality associated with diagnosing and treating FLLs. These will likely include:

- Morbidity and mortality associated with FLLs
- Biopsy-related morbidity
- Liver resection-related mortality and morbidity
- Radiation-induced cancer from CT with contrast. Scoping workshop attendees felt that the additional risk of cancer, when compared to the general population, from radiation induced cancer from CT with contrast scans was likely to be insignificant as individuals were likely to present in later life and were unlikely to undergo multiple scans.
- Nephrotoxicity from contrast agents used in CT/MRI.
- Any side effects or complications arising from the use of SonoVue
- Adverse events associated with chemotherapy.

These outcomes will all be included in an estimate of health related quality of life.

### 5.6 Cost considerations

The equipment needed to perform a CEUS scan is assumed to be readily available in the NHS in England. An unknown proportion of ultrasound scanners will likely require a software upgrade estimated to cost £4-7000 in order to conduct a CEUS scan.

# 6 Modelling approach

#### 6.1.1 Existing models

One existing economic model that reported costs and QALYs for the use of SonoVue in the characterisation of FLLs was identified during scoping (personal communication from the external assessment group). Also, cost-effectiveness information on costs per diagnostic examination (CEUS, CT with contrast, MRI with contrast and histology/biopsy) or cost per detected malignancy can be found and may be useful for the assessment.

#### 6.1.2 Potential diagnostic strategies

Depending on the nature of the FLL and local practice within the NHS a range of typical diagnostic strategies may emerge. For current practice these include:

**Current practice**

1. B-Mode / Colour-Doppler → CT with contrast* → biopsy *
2. B-Mode / Colour-Doppler → MRI with contrast* → biopsy *
3. B-Mode / Colour-Doppler → CT with contrast* → MRI with contrast * → biopsy *
4. B-Mode / Colour-Doppler → MRI with contrast* → CT with contrast * → biopsy *

* additional examination, if previous one was inconclusive

Clinical experts suggest that current practice for the detection and characterisation of FLLs in the NHS in England may involve performing these tests in other sequences. It is possible that some individuals may begin by having lesions detected with MRI or CT with contrast, but with the tests not being given in a manner to permit characterisation of the lesion. Individuals may have the tests in sequences other than those listed in the strategies above. Although the decision about which of MRI with contrast or CT with contrast to use as the next imaging modality following the initial ultrasound scan is likely to be dependent on local availability, MRI with contrast has a better sensitivity and specificity than CT with contrast for the detection and characterisation of FLLs.

Given the above strategies the following strategies have been proposed as likely ways to use CEUS for the detection and characterisation of FLLs.

**Proposed practice (plus CEUS)**

5. B-Mode / Colour-Doppler → CEUS* → CT with contrast* → biopsy *
6. B-Mode / Colour-Doppler → CEUS* → MRI with contrast* → biopsy *
7. B-Mode / Colour-Doppler → CEUS* → CT with contrast* → MRI with contrast * → biopsy *
8. B-Mode / Colour-Doppler → CEUS* → MRI with contrast* → CT with contrast * → biopsy *

* additional examination, if previous one was not conclusive

The diagnostic strategies outlined above are a sample of some of the most common strategies used in the NHS in England (strategies 1 – 4) and how these strategies may be modified with the addition of CEUS (strategies 5 – 8). The assessment should identify and model the full list of potential strategies that may be used for the detection and characterisation of FLLs, of which the cost-effective strategies are identified. The role of SonoVue in monitoring treatment of FLLs should also be modelled if data are available.

### 6.1.3 Model structure

Published studies that measure the clinical utility of SonoVue/CEUS from initial diagnosis through to final health outcomes have not been identified during the scoping phase. Consequently, it is likely that a linked evidence approach will need to be used in the modelling. That is, outcomes of the diagnostic tests to be assessed will need to be related to changes in final heath outcomes.

### 6.1.4 Health outcomes

QALYs will need to be calculated from the economic modelling.

## 7 Equality issues

No potential equality issues have been identified during the preparation of the scope.

## 8 Implementation issues

No potential implementation issues have been identified during the preparation of the scope.

# Appendix A Glossary

**Contrast agent**
A contrast medium (or contrast agent) is a chemical substance applied to the anatomical or functional region being imaged, to increase the differences between different tissues or between normal and abnormal tissue.

**Echocardiography**
Echocardiography is the ultrasound examination of the heart. Depending on the used ultrasound system, echocardiograms can be two-dimensional slices or 3D real-time images of the heart.

**Focal Liver Lesion (FLL)**
Focal lesion in the liver describes any tissue abnormality occurring in one specific area of the liver.

**Histology**
The science concerned with the structure of organ tissues, including the composition of cells and their organization into various body tissues. The tissue of interest is often collected by performing a biopsy.

**Market Authorisation**
Medicines which meet the standards of safety, quality and efficacy are granted a marketing authorisation (by the MHRA/EMEA), which is normally necessary before they can be prescribed or sold. This authorisation covers all the main activities associated with the marketing of a medicinal product.

**Macrovasculature**
The portion of the circulatory system composed of the largest vessels, such as the cerebral arteries.

**Microvasculature**
The portion of the circulatory system composed of the smallest vessels, such as the capillaries, arterioles, and venules.

**Nephrotoxicity**
The quality or state of being toxic to kidney cells.

**Ultrasound**
Ultrasound (also called ultrasonography) uses equipment that generates high frequency sound waves to produce images from muscles, soft tissues, fluid collections, and vascular structures of the human body. Ultrasound visualizes anatomy, function, and pathology of various parts of the body.

## Appendix B Abbreviations

| | |
|---|---|
| AASLD | American Association for the Study of Liver Diseases |
| CEUS | Contrast enhanced ultrasound |
| DAP | Diagnostics Assessment Programme |
| EASL | European Association for the Study of the Liver |
| EFSUMB | European Federation of Societies for Ultrasound in Medicine and Biology |
| FLL | Focal liver lesion |
| HCC | Hepatocellular carcinoma |
| QALY | Quality adjusted life year |

## Appendix C Related NICE Guidance

**Refer to http://guidance.nice.org.uk/Topic/Cancer/Liver**

# Appendix D References

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## Appendix E Equality Impact Assessment

The impact on equality has been assessed during this assessment according to the principles of the NICE Equality scheme.

| | |
|---|---|
| 1. | Have any potential equality issues been identified during the scoping process (scoping workshop discussion, assessment subgroup discussion), and, if so, what are they? |
| None identified | |

| | |
|---|---|
| 2. | What is the preliminary view as to what extent these potential equality issues need addressing by the Committee? |
| N/A | |

| | |
|---|---|
| 3. | Has any change to the draft scope been agreed to highlight potential equality issues? |
| N/A | |

| | |
|---|---|
| 4. | Have any additional stakeholders related to potential equality issues been identified during the scoping process, and, if so, have changes to the stakeholder list been made? |
| Additional stakeholders have not been identified | |

**Approved by Associate Director (name):** …Nick Crabb……..

**Date:** 07/10/2011

## Appendix F Members of the Assessment Subgroup

| | Name of representative | Job Title | Organisation |
|---|---|---|---|
| **Standing Committee Members** | Mark Kroese | Consultant in Public Health Medicine | Peterborough Primary Care Trust / UKGTN |
| | Steve Thomas | Senior Lecturer and Consultant Radiologist | School of Health & Related Research, University of Sheffield |
| **Specialist Committee Members** | Gail Coster | Advanced Practitioner Sonographer (Trainee Consultant) | Mid Yorkshire Hospitals NHS Trust |
| | Jane Smith | Consultant Sonographer | Leeds & West Yorkshire Radiology Academy |
| | Kofi Oppong | Consultant Gastroenterologist | Newcastle NHS Trust |
| | Richard Hall | Patient Support Group Manager | British Liver Trust |
| | Timothy Hoare | Consultant Radiologist | The Newcastle Upon Tyne Hospitals NHS Foundation Trust |
| | | | |
| | | | |
| **External Assessment Group** | Marie Westwood | | Kleijnen, Systematic Reviews |
| | Ken Redekop | | |
| | Janneke Grutters | | |