

## **Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis**

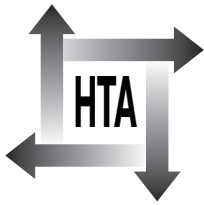
J Thompson Coon, G Rogers, P Hewson,  
D Wright, R Anderson, M Cramp, S Jackson,  
S Ryder, A Price and K Stein



September 2007

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# Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis

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## Abstract

### Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis

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**Objectives:** To evaluate the effectiveness, cost-effectiveness and cost-utility of surveillance of patients with cirrhosis [alcoholic liver disease (ALD)-, hepatitis B (HBV)- and C virus (HCV)-related], using periodic serum  $\alpha$ -fetoprotein (AFP) testing and/or liver ultrasound examination, to detect hepatocellular carcinoma (HCC), followed by treatment with liver transplantation or resection, where appropriate.

**Data sources:** Electronic databases were searched up to March 2006.

**Review methods:** A systematic review was carried out using standard methodological guidelines. A computerised decision-analytic model was then developed to compare various surveillance strategies.

**Results:** No studies were identified that met the criteria of the systematic review. Based on the assumptions used in the model, the most effective surveillance strategy uses a combination of AFP testing and ultrasound at 6-monthly intervals. Compared with no surveillance, this strategy is estimated to more than triple the number of people with operable HCC tumours at time of diagnosis, and almost halves the number of deaths from HCC. On all effectiveness measures and at both testing frequencies, AFP- and ultrasound-led surveillance strategies are very similar. This may be because test sensitivity was varied according to tumour size, which means that AFP testing is capable of identifying many more small tumours than ultrasound. The best available evidence suggests that AFP tests will detect approximately six times as many small tumours as ultrasound. Increasing the frequency of either test to 6-monthly intervals is

more effective than performing combined testing on an annual basis. The undiscounted lifetime cost of the surveillance strategies, including all care and treatment costs, ranges from £40,300 (annual AFP triage) to £42,900 (6-monthly AFP and ultrasound). The equivalent discounted costs are £28,400 and £30,400. Only a small proportion of these total costs results from the cost of the screening tests. However, screening test costs, and the cost of liver transplants and caring for people post-transplant, accounted for most of the incremental cost differences between alternative surveillance strategies. The results suggest that different surveillance strategies may provide the best value for money in patient groups of different cirrhosis aetiologies. The surveillance of people with HBV-related cirrhosis for HCC provides the best value for money, while surveillance in people with ALD-related cirrhosis provides the poorest value for money. In people with HBV-related cirrhosis, at an assumed maximum willingness to pay (WTP) for a quality-adjusted life-year (QALY) of £30,000, both the deterministic and probabilistic cost-utility analyses suggest the optimal surveillance strategy would be 6-monthly surveillance with the combination of AFP testing and ultrasound. In contrast, for those with ALD-related cirrhosis, annual screening with AFP as a triage test is the only surveillance strategy that is likely to be considered cost-effective at this WTP. The probabilistic analysis implies that the estimated benefits of a 6-monthly AFP triage strategy will only be worth the cost in those with ALD when society's WTP for a QALY exceeds around £40,000. For people with HCV-related cirrhosis, the model suggests that the most

cost-effective surveillance strategy at a WTP threshold of £30,000/QALY would be surveillance with a 6-monthly AFP triage strategy.

**Conclusions:** In a mixed-aetiology cohort, the most effective surveillance strategy is to screen each patient with AFP assay and ultrasound imaging on a 6-monthly basis. However, when costs are taken into account it is doubtful whether ultrasound should be routinely offered to those with blood AFP of less than 20 ng/ml, unless policy-makers are prepared to pay over £60,000 per QALY for the benefits achieved. Furthermore, the cost-effectiveness of surveillance for HCC varies

considerably depending on the aetiology of cirrhosis; it is much more likely to be cost-effective in those with HBV-related cirrhosis, and much less likely to be cost-effective in those with ALD-related cirrhosis. Further development of the model would help to enable refinement of an optimal screening strategy. Research into the use of contrast-enhanced ultrasound technology for HCC detection would also be valuable, as would research into the epidemiology and natural history of ALD-related cirrhosis. Studies are also needed to investigate the influence of cirrhosis aetiology on tumour AFP expression.



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## Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

### Glossary

**Alanine transferase** An enzyme present in the liver; levels of which are raised in cases of viral hepatitis.

**Ascites** An accumulation of fluid in the abdomen which may occur as a result of cirrhosis of the liver.

**Cirrhosis** A condition in which the liver responds to injury or death of some of the cells by producing interlacing strands of fibrous tissue between which are nodules of regenerating cells.

**Fibrosis** The formation of fibrous or scar tissue.

**Genotype** The genetic information carried by a pair of alleles which controls a particular characteristic.

**Multinodular** A hepatocellular carcinoma (HCC) tumour type which is either a collection of discrete lesions developing synchronously (multicentric HCC), or one dominant mass and a number of 'daughter' nodules (intrahepatic metastases).

**Quality-adjusted life-year** A measure of health outcome that weights time spent in a health state according to the quality of that health state.

**Sensitivity** The proportion of people who have a disease and are correctly classified as having the disease by a diagnostic test.

**Specificity** The proportion of people who do not have a disease and are correctly classified as not having it by a diagnostic test.

**Uninodular** Describes a single HCC tumour in one place (sometimes called a solitary HCC tumour).

**Utility** A measure of the value attached to a health state. Used to weight time spent in that health state in cost-utility analyses.

**Variceal bleeding** Occurs as a result of increased pressure in the portal vein leading to the development of large veins across the oesophagus and stomach which become fragile and can bleed easily.

**List of abbreviations**

AA	authors' assumption	MRI	magnetic resonance imaging
AFP	alpha-fetoprotein	NA	not applicable
ALD	alcoholic liver disease	NICE	National Institute for Health and Clinical Excellence
CEAC	cost-effectiveness acceptability curve	NNS	number needed to be under surveillance
CEUS	contrast-enhanced ultrasound	NR	not reported
CI	confidence interval	NS	not stated
C-P	Child–Pugh	NSRC	National Schedule of Reference Costs
CT	computed tomography	OLT	orthotopic liver transplantation
DCP	des-gamma carboxyprothrombin	ONS	Office for National Statistics
EO	expert opinion	PEI	percutaneous ethanol injection
EQ-5D	EuroQol 5 Dimensions	PLC	primary liver cancer
EVPI	expected value of perfect information	PSA	probabilistic sensitivity analysis
HBV	hepatitis B virus	QALY	quality-adjusted life-year
HCC	hepatocellular carcinoma	RCT	randomised controlled trial
HCC <sub>L</sub>	large HCC tumour	RFA	radiofrequency thermal ablation
HCC <sub>M</sub>	medium-sized HCC tumour	SD	standard deviation
HCC <sub>S</sub>	small HCC tumour	SF-36	(Medical Outcomes Study) Short Form 36
HCV	hepatitis C virus	SG	standard gamble
HRQoL	health-related quality of life	SR	systematic review
HUI	Health Utility Index	TACE	transarterial chemoembolisation
ICER	incremental cost-effectiveness ratio	TNM	tumour node metastasis
IQR	interquartile range	UKT	UK Transplant
ITT	intention-to-treat	US	ultrasound
LUS	liver ultrasound (examination)	WTP	willingness to pay
MELD	Model for End-stage Liver Disease		

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.



## Executive summary

### Background

Cirrhosis is long-term liver damage from the build-up of scar tissue (fibrosis) which, as it develops, impairs effective blood flow and inhibits the organ's vital functions. There are many causes of cirrhosis, including viral hepatitis [hepatitis B and C virus (HBV and HCV)], excessive alcohol intake, non-alcoholic fatty liver disease, primary biliary cirrhosis and haemochromatosis (iron overload).

Cirrhosis can remain in an asymptomatic (compensated) state for many years. The onset of overt liver failure (decompensation) is characterised by a variety of symptoms including ascites, portosystemic encephalopathy, gastrointestinal bleeding and hepatorenal syndrome, and is often the first indication of previously silent liver disease.

Hepatocellular carcinoma (HCC) is a malignant tumour arising from liver cells (hepatocytes) and occurs mainly in cirrhotic livers. HCC affects around twice as many men as women and is more common in those above the age of 40. There is some evidence for a recent rise in incidence of HCC in England with age-adjusted incidence rising from 1.8 per 100,000 men and 0.6 per 100,000 women in 1995 to 2.8 and 0.8, respectively, in 2002. Curative treatment options include resection and orthotopic liver transplantation. Palliative treatments include percutaneous ethanol injection, radiofrequency ablation and transarterial chemoablation.

Two diagnostic tests are routinely used to detect HCC in clinical practice: serum  $\alpha$ -fetoprotein (AFP) and ultrasonography. The sensitivity of AFP as a diagnostic tool is restricted by the existence of non-AFP-secreting tumours. The reliability of ultrasonographic diagnosis depends on a range of factors, including the expertise of the operator, the sophistication of the equipment and the size and nature of the tumour.

Routine periodic surveillance of individuals with cirrhosis is currently recommended by UK, European and American clinical guidelines. A 2002 survey confirmed that approximately three-quarters of UK gastroenterologists undertake a

formal programme of surveillance for HCC in cirrhosis, mostly using a combination of AFP and ultrasound. The optimal screening frequency has not been established, although an interval of 6 months is recommended in UK and European guidelines, purportedly on the basis of available evidence on tumour growth rate.

Observational data suggest that HCCs detected during formal surveillance are smaller and more likely to be a single lesion than those that present symptomatically or by chance. Consequently, patients whose disease is detected as a result of surveillance are more likely to receive curative treatment than those whose diagnosis is symptomatic or incidental.

### Objective

The objective of this report was to evaluate the effectiveness, cost-effectiveness and cost-utility of surveillance of patients with cirrhosis [alcoholic liver disease (ALD)-, HBV- and HCV-related], using periodic serum AFP testing and/or liver ultrasound examination, to detect HCC, followed by treatment with liver transplantation or resection, where appropriate.

### Methods

#### Systematic review

Electronic databases were searched for randomised clinical trials of surveillance (with AFP and ultrasound) of people with cirrhosis of known underlying cause (ALD, HBV, HCV) for HCC. Updated searches were performed in March 2006.

#### Economic analysis

A computerised decision-analytic model was developed to compare various surveillance strategies. Comparisons were made between:

- no surveillance
- annual surveillance using AFP as the initial screening test
- annual surveillance using ultrasound alone
- annual surveillance using AFP and ultrasound
- 6-monthly surveillance using AFP as the initial screening test

- 6-monthly surveillance using ultrasound alone
- 6-monthly surveillance using AFP and ultrasound.

The study modelled a population with a diagnosis of compensated cirrhosis who are also eligible to enter a surveillance programme. Those deemed eligible were aged 70 years or less, with no pre-existing medical conditions that would preclude treatment with liver transplantation or hepatic resection (including current alcohol or intravenous drug abuse).

Previously published research and a panel of clinical experts helped to inform the structure of the model. A Markov model was used to capture both natural disease progression and diagnostic and treatment pathways reflective of current best clinical practice in the UK NHS. HCC tumours are detected as a result of regular surveillance and symptomatic or incidental diagnosis. Surgical treatment of small or medium-sized tumours is predominantly by liver transplantation; liver resection is also possible, particularly in people with small tumours. Surgical treatment of people with large tumours is not possible within the confines of the model. People with decompensated cirrhosis or a surgically treatable tumour enter the transplant waiting list and have an equal chance of receiving a liver transplant. People deemed to have surgically untreatable HCC enter a range of simpler model states which simulate the costs and effectiveness of palliative care and best supportive care.

Parameter estimates were obtained from comprehensive literature reviews. No methodological restrictions were applied, but searches were limited to papers published or available in English.

The technical performance of the alternative testing strategies was modelled using decision trees. Test sensitivity for AFP and ultrasound was varied according to tumour size. Expected costs and utilities for each surveillance strategy were calculated using both a cohort and a Monte Carlo simulation approach. The model runs for the lifetime of the cohort. Costs (base year 2004) and benefits (QALYs) were discounted at 3.5%.

The model was developed to allow separate analysis of each of the three main cirrhosis aetiologies (ALD, HBV and HCV).

Uncertainty in the model was explored using extensive one-way sensitivity analyses, selected scenario analyses and probabilistic sensitivity

analysis. A value of information analysis was conducted to determine the maximum possible value of further research.

## Results

### Systematic review

The searches returned 214 separate references. From screening of abstracts, 207 of these were excluded, leaving seven potentially relevant studies to be reviewed in full. All seven were excluded at this stage [no results for patients with cirrhosis ( $n = 3$ ), modelling study ( $n = 1$ ), narrative review ( $n = 2$ ), uncontrolled cohort study ( $n = 1$ )].

### Economic analysis

#### Effectiveness of surveillance

Based on the assumptions used in the model, the most effective surveillance strategy uses a combination of AFP testing and ultrasound at 6-monthly intervals. Compared with no surveillance, this strategy is estimated to more than triple the number of people with operable HCC tumours at time of diagnosis, and almost halve the number who die from HCC. This is a result of the identification of over ten times as many small HCC tumours (less than 2 cm in diameter) and over twice as many medium-sized tumours (between 2 and 5 cm in diameter). Consequently, more tumours are suitable for surgical intervention. Under the conditions of the model, this surveillance strategy would lead to an increase in the percentage of liver transplantations performed for known HCC (as opposed to decompensated cirrhosis) from 8% to 28%, compared with no surveillance.

On all effectiveness measures and at both testing frequencies, AFP- and ultrasound-led surveillance strategies are very similar. This may be because test sensitivity was varied according to tumour size, which means that AFP testing is capable of identifying many more small tumours than ultrasound. The best available evidence suggests that AFP tests will detect approximately six times as many small tumours as ultrasound. Increasing the frequency of either test to 6-monthly intervals is more effective than performing combined testing on an annual basis.

#### Cost of surveillance

The undiscounted lifetime cost of the surveillance strategies, including all care and treatment costs, ranges from £40,300 (annual AFP triage) to £42,900 (6-monthly AFP and ultrasound). The equivalent discounted costs are £28,400 and

£30,400. Only a small proportion (<4% of undiscounted costs) of these total costs results from the cost of the screening tests. However, screening test costs, and the cost of liver transplants and caring for people post-transplant, accounted for most of the incremental cost differences between alternative surveillance strategies.

### **Cost-effectiveness of surveillance**

The results suggest that different surveillance strategies may provide the best value for money in patient groups of different cirrhosis aetiologies. The surveillance of people with HBV-related cirrhosis for HCC provides the best value for money, while surveillance in people with ALD-related cirrhosis provides the poorest value for money.

In people with HBV-related cirrhosis, at an assumed maximum willingness to pay (WTP) for a quality-adjusted life-year (QALY) of £30,000, both the deterministic and probabilistic cost-utility analyses suggest the optimal surveillance strategy would be 6-monthly surveillance with the combination of AFP testing and ultrasound.

In contrast, for those with ALD-related cirrhosis, annual screening with AFP as a triage test is the only surveillance strategy that is likely to be considered cost-effective at this WTP. NHS investment in more effective surveillance strategies probably represents an unacceptable cost for the extra benefits gained (e.g. £35,000 per QALY gained by moving to a 6-monthly AFP triage strategy). In addition, there is a high degree of uncertainty in the ALD model. The probabilistic analysis implies that the estimated benefits of a 6-monthly AFP triage strategy will only be worth the cost when society's WTP for a QALY exceeds around £40,000.

For people with HCV-related cirrhosis, and again applying this WTP threshold, the model suggests that the most cost-effective surveillance strategy would be surveillance with a 6-monthly AFP triage strategy.

It may not be considered practical to have separate screening strategies for people with cirrhosis of different aetiology. Results for an artificially produced mixed cohort containing people with HBV, ALD and HCV suggest that, if one surveillance policy had to be applied across cirrhosis cohorts of all three aetiologies, 6-monthly AFP with ultrasound is always the most effective option and, at commonly accepted levels of WTP

for QALYs, 6-monthly AFP as a triage test is the most cost-effective strategy.

These results should be viewed with caution for a number of reasons. Considerable uncertainty still surrounds some of the underlying parameters that influence the cost-effectiveness estimates. In addition, some of the differences between aetiologies may be more attributable to the mean age at diagnosis than to any inherent differences in the nature of disease progression. Lastly, the discounting of costs and benefits has a major impact on the cost-effectiveness results.

## **Conclusions**

In a mixed aetiology cohort, the most effective surveillance strategy is to screen each patient with AFP assay and ultrasound imaging on a 6-monthly basis. However, when costs are taken into account it is doubtful whether ultrasound should be routinely offered to those with blood AFP of less than 20 ng/ml, unless policy makers are prepared to pay a very high price (over £60,000 per QALY) for the extra benefits achieved. Furthermore, the cost-effectiveness of surveillance for HCC varies considerably depending on the aetiology of cirrhosis; it is much more likely to be cost-effective in those with HBV-related cirrhosis, and much less likely to be cost-effective in those with ALD-related cirrhosis. This may be largely due to the younger age at diagnosis of cirrhosis in patients with HBV. This raises the possibility that there may be further subgroups of patients with ALD and HCV, diagnosed with cirrhosis at a younger age, in whom more intensive surveillance might provide value for money.

### **Implications for policy**

The results show that surveillance strategies for HCC are effective, and can often be considered cost-effective in patients with cirrhosis. We believe that the implementation of formal surveillance programmes should be considered where they do not currently exist.

The results also suggest that different surveillance strategies in patient groups with different underlying causes of cirrhosis may provide the best value for money, if appropriate recall systems could be implemented, and also if this was judged to be ethically acceptable.

A surveillance strategy in which AFP testing is used as a triage step probably represents the best value for money.

These results also suggest a possible shift in the clinical settings where cirrhosis surveillance is conducted; as AFP triage appears to be a highly cost-effective strategy, either annually or 6-monthly, it may be more appropriate to perform the initial screening test in the primary care setting.

If effective surveillance programmes were to become widespread across the UK against a background of limited organ supply, the waiting list for liver transplants would undoubtedly increase. Detailed exploration of this was beyond the scope of this project, but preliminary findings suggest that this might be an important issue.

## Recommendations for further research

### Model development

- Extensive value of information analysis should be used to identify which parameters or groups of parameters contribute most to the uncertainty in the cost–utility results, and therefore suggest priorities for further primary research.
- Alternative modelling methods should be used to account for heterogeneity in the patient population, so that the impact of factors such as tumour growth rate, tumour characteristics and variability in individual patients' serial test results may be accurately assessed. Such methods could also be used to investigate the optimal surveillance strategy, optimal surveillance interval and the effects of surveillance on waiting lists for liver transplantation.
- Further investigation is needed into the accepted cut-off levels for AFP tests and how different cut-off levels impact on the effectiveness and cost-effectiveness of surveillance for HCC.
- Further modelling studies should investigate innovative surveillance strategies not currently undertaken in clinical practice.
- Further modelling studies should investigate the impact of alternative treatment modalities (e.g. more resection of small tumours, radiofrequency ablation as a 'curative' treatment

of small tumours), because identifying more operable HCC tumours will probably lead to longer transplant waiting lists.

- Further modelling is needed of the impact of age at diagnosis of cirrhosis on the cost-effectiveness of surveillance strategies.
- Anecdotal reports suggest that non-alcohol fatty liver disease is increasing in incidence and will soon represent the second largest cause of cirrhosis in the UK. Further modelling studies are needed to assess the effectiveness and cost-effectiveness of surveillance in this patient group.

### Other research

- The effectiveness and cost-effectiveness of microbubble ultrasound technology to detect HCC tumours should be evaluated, and the test performance in various stages of cirrhosis/aetiologies compared with explant pathology.
- Epidemiological research in the UK is needed to assess the incidence and rate of tumour growth of HCC in different cirrhosis aetiologies.
- The association between the level of AFP secreted and tumour size in different cirrhosis aetiologies needs to be assessed.
- Detailed observational research is needed on the epidemiology and natural history of ALD-related cirrhosis. Despite existing evidence that ALD accounts for the majority of the UK's disease burden of cirrhosis, and emerging evidence that alcohol consumption is rising, ALD-related cirrhosis remains particularly poorly described in the literature.
- Observational studies could be conducted which collect AFP measurements on the same population of people with cirrhosis over time, and investigate the relationship between the emergence or presence of HCC tumours and patterns of change in AFP levels over time (as opposed to the predictive ability of particular absolute AFP thresholds).
- Quality of life studies should assess the utility of all stages of disease, during assessment for treatment, during and post-treatment in all cirrhosis aetiologies in a UK population.

# Chapter I

## Aim and background

### Aim

The aim of this research was to determine the effectiveness, cost-effectiveness and cost-utility of surveillance of patients with cirrhosis, using periodic serum alpha fetoprotein (AFP) testing and/or ultrasound examination, to detect hepatocellular carcinoma (HCC), followed by treatment with liver transplantation or resection, where appropriate.

The assessment protocol is reproduced in full in Appendix 1.

### Epidemiology and natural history of hepatic cirrhosis

Although the liver is extremely efficient at recovering from isolated insults, exposure to long-term damage results in the build-up of scar tissue (fibrosis) which, as it develops, impairs effective blood flow and inhibits the organ's vital functions, including its ability to regenerate itself. The progressive, irreversible form of this liver disease is referred to as cirrhosis, a term that derives from an ancient Greek word, *kirrhos* (orange-coloured), in reference to the distinctive appearance of affected livers at autopsy.

### Aetiology

Hepatic cirrhosis can have a wide variety of causes, by far the most common of which are viral hepatitis [hepatitis B virus (HBV) and hepatitis C virus (HCV)] and alcoholic liver disease (ALD). The relative importance of these factors is heavily dependent on geography: in most industrialised countries, alcoholic aetiology predominates whereas, in most of the developing world and Mediterranean Europe, postviral cirrhosis is more common.

### Hepatitis B

In adults, the great majority of HBV infections are either silent or predisposed to swift recovery, but a proportion of affected people will subsequently develop 'carrier' status (more properly, chronic, asymptomatic HBV infection). It is these people who are at risk of developing hepatic cirrhosis. The rate of cirrhosis development in patients with

chronic HBV is estimated to be in the range 2–5.4 per 100 person-years, with a 5-year cumulative incidence of cirrhosis of 8–20%.<sup>1</sup>

HBV prevalence in the UK is low, with a lifetime risk of infection estimated at between 0.4<sup>2</sup> and 0.55%.<sup>3</sup> It is estimated that around 0.5 per 100,000 UK residents develop chronic HBV each year, with a lifetime risk in the region of 0.04–0.05%.<sup>2,3</sup> HBV therefore makes a relatively minor contribution to cirrhosis in the UK: a 1985 cross-sectional analysis of patients with cirrhosis in London suggested that 7.7% had chronic HBV infection,<sup>4</sup> and a more recent survey from Birmingham identified just 4.5% of patients with the virus.<sup>5</sup> These proportions are consistent with those reported in other countries with a low prevalence of HBV: 4.2% in France,<sup>6</sup> 7% in the USA<sup>7</sup> and 7.5% in Spain,<sup>8</sup> and much lower than estimates from areas with higher HBV endemicity, for example 13% in Italy,<sup>9</sup> 20% in Japan,<sup>10</sup> 58% in Korea,<sup>11</sup> 63.3% in central Africa<sup>12</sup> and 74.5% in China.<sup>13</sup>

### Hepatitis C

As with HBV, the acute phase of HCV infection is predominantly asymptomatic. However, rates of chronicity are much higher in HCV: only about 20% of infected patients clear the virus, and the remaining proportion are subject to variable progression of liver inflammation and fibrosis which may culminate in cirrhosis.<sup>14</sup> This process can be reflected in symptomatic presentation (nausea, anorexia, chronic fatigue) but, more often, it is clinically silent until the liver is quite extensively damaged.<sup>15</sup> The rate at which chronic HCV infections progress to cirrhosis depends on an array of factors. Freeman and colleagues meta-analysed 57 studies addressing this issue, concluding that the key markers of accelerated development of cirrhosis are male gender, heavy alcohol use, elevation of alanine aminotransferase (ALT, an important biological marker of liver function) and degree of liver inflammation. Their predictive model suggests that, 20 years after HCV infection, the rate of progression to cirrhosis ranges from 10% in low-risk individuals to 25% in high-risk cases.<sup>16</sup> In retrospective analyses of patients with cirrhosis, including one based on a Scottish population,<sup>17</sup> it is estimated that

progression to cirrhosis occurs a median of 30–35 years after infection with HCV.<sup>18,19</sup>

The World Health Organization (WHO) estimates that about 3% of the world's population has been infected with HCV, leading to around 170 million chronically infected cases globally. Geographical distribution appears to be quite sporadic, but broadly follows the trend of lower prevalence in richer countries.<sup>20</sup> In relative terms, the UK has very low prevalence of HCV. The Department of Health's HCV strategy assumes that 0.4% of the general population in England have chronic HCV infection,<sup>14</sup> although this is thought to be a conservative estimate.<sup>21</sup> The main route of transmission, since the introduction of effective screening of blood products, is the sharing of blood-contaminated needles in injecting drug users.

There are limited data on the role played by HCV in the aetiology of cirrhosis in the UK. One published analysis reports that 7.6% of cirrhotoses detected in a single Birmingham unit were associated with HCV positivity.<sup>5</sup> Although this estimate is based on a relatively small sample, it is notable that the proportion is extremely low in comparison with those reported in other countries: 17% in France,<sup>6</sup> 21% in Belgium,<sup>22</sup> 27–35% in the USA,<sup>7,23</sup> 29% in Spain,<sup>8</sup> 51% in Africa,<sup>24</sup> 58% in Japan<sup>25</sup> and 69.9% in Italy.<sup>9</sup>

### Alcohol

It is estimated that approximately 10–20% of chronic heavy drinkers develop cirrhosis in their lifetime.<sup>26</sup> There is conflicting evidence as to whether alcohol exerts a dose–response<sup>27,28</sup> or threshold<sup>29,30</sup> effect, although it appears that there is generally little danger in low levels of alcohol consumption [fewer than 30 g (around 4 units) of alcohol per day<sup>31</sup>]. Predominant consumption of spirits<sup>32,33</sup> (especially illicit, home-made liquor<sup>34</sup>) may exacerbate the risk. Conversely, a drinking pattern dominated by meal-time consumption may be associated with lower rates of disease.<sup>31</sup>

It has been suggested that up to 80% of all UK cirrhotoses are related to a history of heavy alcohol consumption,<sup>35</sup> although studies based on hospital admission statistics suggest the true proportion is around 60%.<sup>5,36</sup> Such findings fit well with the 60.5% reported by an extensive cohort study based on mortality statistics from Denmark,<sup>37</sup> a country with similar drinking patterns to the UK<sup>38</sup> and comparable prevalence of HBV<sup>39</sup> and HCV.<sup>20</sup> Broadly speaking, the proportions of alcohol-related cases reported from other countries are inversely associated with the prevalence of viral

hepatitis: 69.5% in France,<sup>6</sup> 61% in Belgium,<sup>22</sup> 60.5% in Denmark,<sup>37</sup> 59% in Spain,<sup>8</sup> 35% in the USA,<sup>23</sup> 31.9% in Italy<sup>9</sup> and 21.9% in Japan.<sup>40</sup>

It should be noted that these risk factors are not mutually exclusive. The combination of HCV infection and alcohol misuse, in particular, appears to constitute a potent interaction in the development of cirrhosis.<sup>19,41,42</sup>

There are several other risk factors for the development of cirrhosis: liver damage secondary to obesity<sup>43</sup> and spontaneous degeneration of the bile ducts (primary biliary cirrhosis). Haemochromatosis, autoimmune disease and metabolic disease may also be important precursors for the development of cirrhosis. Finally, it should be acknowledged that, although the proportion diminishes as knowledge advances, some cirrhotoses are still classified as 'cryptogenic' (i.e. of unknown cause).

### Incidence

Because cirrhosis frequently goes undetected, it is extremely challenging to provide an accurate estimate of its overall prevalence. Several investigators have studied the proportion of cirrhotic livers among extensive series of autopsies; those from northern and eastern Europe suggest a prevalence of 2–6%,<sup>44–48</sup> although the rate reached 9.5% in Italy.<sup>49</sup>

### Natural history

Because of the liver's relative resilience, cirrhosis can remain in an asymptomatic (compensated) phase for many years. The onset of overt liver failure (decompensation) is characterised by a variety of symptoms, including the following:

- **Ascites** (abdominal swelling caused by the accumulation of fluid within the peritoneal cavity) is the most common presenting symptom.<sup>50–52</sup> This can lead to further complications, including pleural effusions, hernias and, most seriously, spontaneous bacterial peritonitis. In patients with compensated cirrhosis, the 5-year cumulative incidence of ascites is approximately 30%. Once ascites develops, 1-year survival is about 50%.<sup>53</sup>
- **Portosystemic encephalopathy** is a neuropsychiatric condition, which arises as a result of imperfect liver function and secondary circulatory complications, leading to increased exposure to neurotoxic substances in the cerebral bloodflow. The incidence of overt hepatic encephalopathy among patients with



compensated cirrhosis has been estimated at 17.4%,<sup>54</sup> although subclinical neuropsychiatric dysfunction has been demonstrated in 30–84% of patients with cirrhosis.<sup>55</sup>

- **Gastrointestinal bleeding:** because of the back-pressure caused by obstructed portal veins, varices (dilated veins, which are susceptible to rupture) commonly develop in the oesophagus. Oesophageal varices develop in 50–60% of patients with liver cirrhosis, and up to one-third of these patients have a variceal haemorrhage within 2 years of diagnosis.<sup>53,56</sup>
- **Hepatorenal syndrome:** renal failure secondary to hepatic dysfunction occurs in 40% of patients with cirrhosis and ascites over 5 years.<sup>57</sup>

The most widely used summary measure of decompensation is the Child–Pugh score. Proposed by Child and Turcotte in 1964<sup>58</sup> and modified by Pugh and colleagues in 1973,<sup>59</sup> the score provides a simple system for stratifying liver failure. It subdivides patients into three categories on the basis of a composite score built from five assessments: jaundice (measured by serum bilirubin), liver synthetic function [measured by serum albumin and prothrombin time and/or international normalised ratio (INR)] and overt symptoms (ascites and encephalopathy). The benchmarks that make up the score are shown in *Table 1*.

It has been demonstrated that Child–Pugh scores correlate well with prognosis. The proportion of patients surviving for 5 years from first onset of overt symptoms is 52–70% for grade A patients, 32–50% for grade B patients and 2–36% for

grade C patients, with more recent studies providing estimates at the top end of these ranges.<sup>60–63</sup>

### Incidence of decompensation

Studies of Western cohorts with viral cirrhosis have reported that around 20% of patients develop decompensation within 5 years of diagnosis<sup>64–67</sup> (although it should be emphasised that many of these patients will have had an extended prehistory of silent cirrhosis). There is some suggestion that patients with HCV-related cirrhosis are more likely to develop decompensation than those with HBV (5-year cumulative incidence of 28% and 16%, respectively;  $p = 0.0094$ ).<sup>67</sup>

Symptomatic decompensation is often the first indication of previously silent liver disease. Cohort studies suggest a high but variable proportion of patients presenting in a decompensated state.<sup>11,62,68</sup> Underlying aetiology may be a significant factor in this variability, with viral cirrhotoses being detected at an earlier stage<sup>69</sup> and patients with cirrhosis of alcoholic origin presenting with more advanced failure.<sup>11,60</sup>

## Epidemiology and natural history of hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the name given to tumours arising from liver cells (hepatocytes). HCC is considered to be the most common type of primary liver tumour, although data from the office for National Statistics (ONS) show that, in England, intrahepatic bile duct

**TABLE 1** Child–Pugh score for chronic liver disease

	Scores		
	1	2	3
Total serum bilirubin level	<2 mg/dl (<34 µmol/l)	2–3 mg/dl (34–51 µmol/l)	>3 mg/dl (>51 µmol/l)
Serum albumin level	>3.5 g/dl (35 g/l)	2.8–3.5 g/dl (28–35 g/l)	<2.8 g/dl (<28 g/l)
INR (prothrombin time)	<1.70 (<4 s)	1.71–2.20 (4–6 s)	>2.20 (>6 s)
Ascites	None	Controlled medically	Poorly controlled
Encephalopathy	None	Controlled medically	Poorly controlled
Total score for five measures: 5–6, Child–Pugh class A (compensated liver disease); 7–9, Child–Pugh class B (decompensated liver disease); 10–15, Child–Pugh class C (end-stage liver disease).			

cancer (cholangiocarcinoma) may be more common,<sup>70</sup> certainly among women.

## Aetiology

HCC is unusual among cancers, since its aetiology is well understood. Overwhelmingly, the premalignant condition is hepatic cirrhosis. In British narrative reviews of HCC, it is commonly asserted that around 80% of tumours develop in cirrhotic livers.<sup>71–73</sup> This figure is in line with the results of a few small UK series from the 1980s, in which rates of 73–80% were reported,<sup>74–76</sup> and comparable with data from elsewhere in Europe (71–88% in France,<sup>77–80</sup> 75–90% in Germany,<sup>81–85</sup> 77–97% in Italy<sup>86–92</sup> and 93% in Spain<sup>93</sup>). The picture may be different in North America, where similar studies suggest that the proportion of HCC patients who have cirrhosis is as low as 58%<sup>94</sup> to 63%.<sup>95</sup>

The rate at which cirrhotic livers progress to HCC is one of the key topics under review in the present study, and is addressed in detail below. It is generally asserted that HCCs develop in cirrhotic livers at a rate of approximately 3–5% per year,<sup>73,96,97</sup> although it is acknowledged that rates may vary according to the aetiology of underlying liver disease. Fattovich and colleagues pooled data on HCC development from a number of cohort studies of European or US patients with cirrhosis (compensated at trial entry; no antiviral treatment). They calculated the annual rate of progression to be around 2.2% in HBV-related cirrhosis, 3.7% in HCV-positive patients and 1.7% in alcohol-related cases.<sup>67,98,99</sup>

In postviral cirrhosis, there is some suggestion that the genotype of the virus may be related to carcinogenesis. Evidence is strongest in HCV, in which genotype 1b appears to be associated with an increased risk of HCC.<sup>100–102</sup> There is little evidence surrounding the relationship between viral genotype and carcinogenesis in HBV. A study from Taiwan suggests that genotype C may be more carcinogenic; however, this genotype is uncommon in Western populations.<sup>103</sup>

A variety of other factors is linked to hepatocellular carcinogenesis:

- **Oral contraceptives** have been associated with increased risk of HCC. Yu and Yuan meta-analysed eight case-control studies conducted in relatively young US white and European women (predominantly without cirrhosis), calculating an odds ratio of 2.5 [95% confidence interval (CI) 1.7 to 3.5] in those who had used

oral contraceptives compared with those who had not.<sup>104</sup>

- **Smoking** appears to increase the risk of HCC, although this effect may only act synergistically in combination with heavy alcohol consumption.<sup>105</sup>
- **Occupational exposure to vinyl chloride** is also recognised as a significant risk factor for hepatocellular carcinogenesis.<sup>106</sup>

## Incidence

Global data suggest that more than 500,000 new cases of primary liver cancer (PLC) develop each year, equating to an age-adjusted worldwide incidence of 14.97 per 100,000 men and 5.51 per 100,000 women per year.<sup>107</sup> This makes the liver the fifth most common site of primary neoplasia,<sup>108</sup> accounting for an estimated 5.6% of all new cancers worldwide.<sup>107</sup>

By comparison, PLC is less prevalent in the UK. In 2002 (the year for which most recent UK registry data are available), 2248 cases were registered in England, giving an age-adjusted incidence of 3.4 per 100,000. In total, 0.8% of cancer registrations were made under International Classification of Diseases-10 (ICD-10) code C22 (malignant neoplasm of liver and intrahepatic bile ducts), making it only the 23rd most common three-figure code in the registry.<sup>109</sup>

On average, 893 cases of HCC were registered each year in England in 1995–2002, equating to an age-adjusted incidence of 1.5 per 100,000.

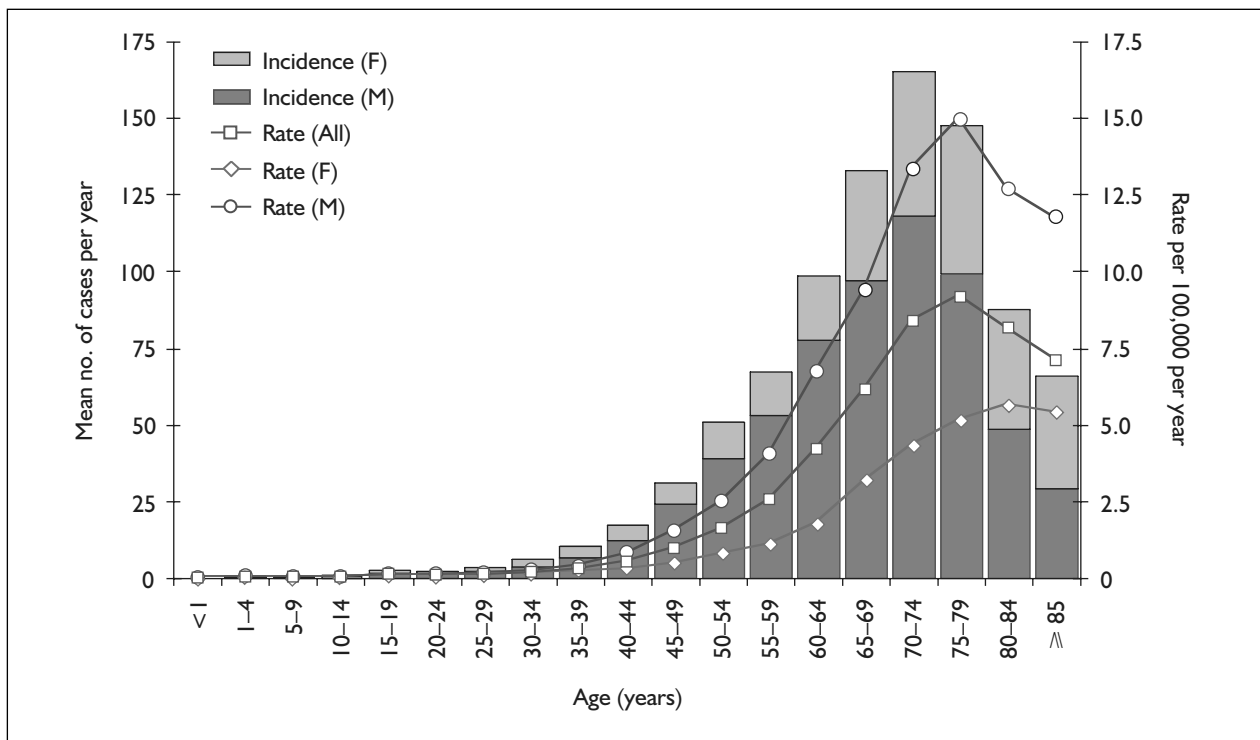
## Demographics

In England, HCC affects around twice as many men as women: in 1995–2002, the male to female ratio was 2.23 ( $\approx$  9:4). The asymmetry peaks in the age group 45–65 years, in which affected men outnumber women by a factor of more than 3.5.

HCC is extremely rare in young people in England: registry data suggest an annual incidence in the order of one per million under-forties. Above the age of 40, incidence increases fairly sharply, to a peak of 14.9 per 100,000 men and 5.1 per 100,000 women in the 75–79 age group (*Figure 1*).

## Time-related trends in incidence and mortality

In recent years, several authors have reported increasing incidence of PLC in general and/or HCC in particular, on the basis of either cancer registries or mortality statistics. There appears to be persuasive evidence in Japanese,<sup>70,110</sup>



**FIGURE 1** Incidence of HCC in England, 1995–2002: distribution by age group. Cases registered under ICD-10 code C22.0 (malignant liver cell carcinoma); data from ONS.<sup>109</sup>

French,<sup>70,79,111,112</sup> Italian,<sup>70,91,112</sup> Australian,<sup>70</sup> Canadian<sup>113</sup> and US<sup>70,114–118</sup> populations.

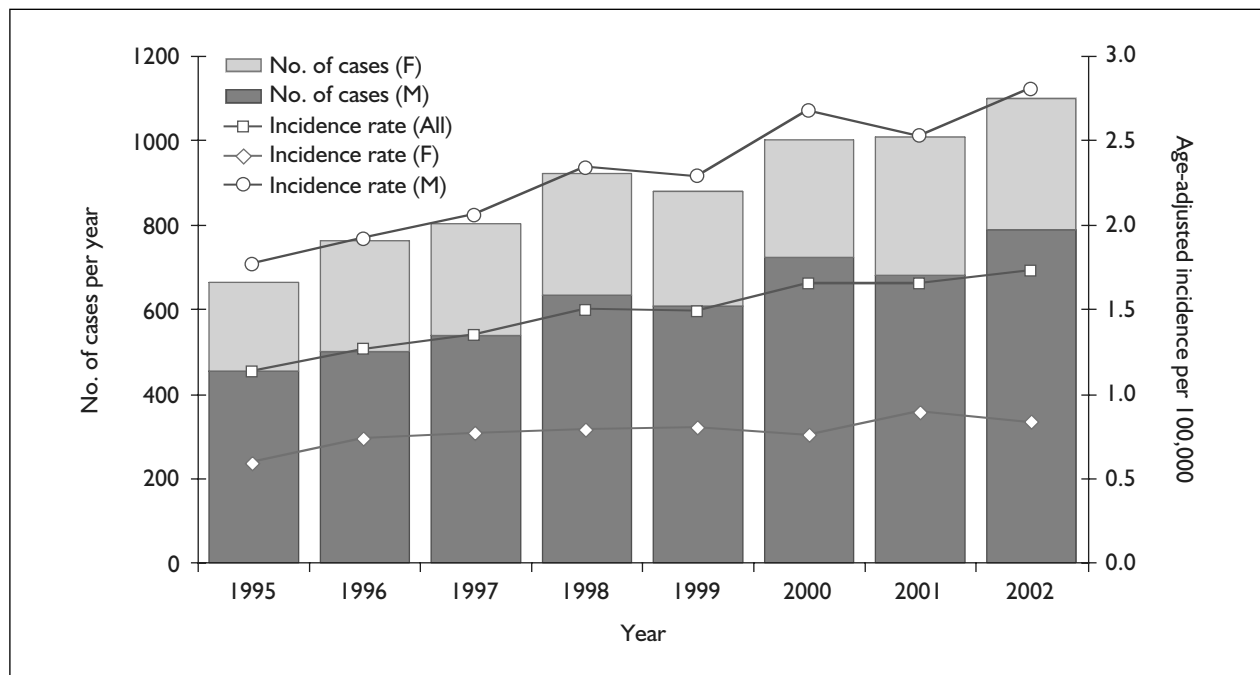
UK data appear to be more ambiguous. Taylor-Robinson and co-workers' review of mortality rates from 1979 to 1994 concluded that, while deaths from all causes of PLC almost doubled in the period, the recorded rates of HCC remained "relatively static"<sup>119</sup> (a finding which has led the same authors to focus attention on the rising incidence of intrahepatic cholangiocarcinoma<sup>120</sup>). La Vecchia and colleagues were unable to detect any consistent trend in PLC mortality in UK data from 1970 to 1996, while recording significant increases over the same period in some other European states,<sup>112</sup> results that are echoed in Khan and colleagues' review of international data from 1979 to 1997.<sup>70</sup>

In contrast, a rising incidence of HCC is an unmistakable feature of the more recent registry data made available to us by the National Cancer Intelligence Centre at the ONS, as shown in *Figure 2*. A steady escalation is apparent, with age-adjusted incidence rising from 1.8 per 100,000 men and 0.6 per 100,000 women in 1995 to 2.8 and 0.8, respectively, in 2002. During this period, the number of registrations of HCC rose by almost two-thirds, from 665 to 1099.

Several hypotheses have been put forward to explain the rising incidence of HCC. Any underlying increase in the prevalence of hepatitis viruses would be expected to result in a commensurate rise in cases of HCC. UK experts are concerned that HCV prevalence is rising. There is also concern that a large reservoir of as-yet undetected cases exists, and many of these individuals are bound to develop symptomatic complications, including HCC.<sup>21,121</sup> In a similar way, increased incidence of HCC is believed to be predominantly attributable to HCV-related cases in North America<sup>113,122,123</sup> and Japan.<sup>124</sup>

Another hypothesis is that, in developed nations, HCC has remained stable in the indigenous population, and the apparent increase is attributable to immigration from populations with higher prevalence of the disease. However, on the basis of one US population, at least, this theory appears unsupported.<sup>117</sup>

Finally, rising incidence of HCC may be contributed to by the substantial improvements in clinical management of chronic cirrhosis in recent years: because fewer patients die of direct complications of cirrhosis,<sup>56,125</sup> more now live to develop HCC.<sup>97,122</sup>



**FIGURE 2** Increasing incidence of HCC in England, 1995–2002. Cases registered under ICD-10 code C22.0 (malignant liver cell carcinoma); data from ONS,<sup>109</sup> direct age-standardisation performed by PenTAG (according to European standard population).

## Pathology

The pathology of HCC can be subdivided according to a wide variety of characteristics and schema.

The gross morphology of the tumour is a key starting point. Solitary (uninodular) tumours are the simplest form of HCC, with a single lesion developing in one place. Multinodular HCCs can either be a collection of discrete lesions developing synchronously (multicentric HCC) or one dominant mass and a number of ‘daughter’ nodules (intrahepatic metastases).<sup>126</sup> Diffuse HCCs are poorly defined, widely infiltrative masses that present particular diagnostic challenges on imaging. Massive tumours are a special instance of a solitary HCC, in which most or all of one lobe of the liver has been replaced. Small ‘satellite’ nodules may be present elsewhere.<sup>127</sup>

There are many other pathological features of HCCs that are considered significant. Histological differentiation (the degree to which the microscopic appearance of HCC cells is recognisably comparable to that seen in normal hepatocytes) seems to be an indication of the maturity of the tumour. Early HCCs are well differentiated, whereas later HCC progression is associated with decreasing differentiation of tumour histology.<sup>128</sup> Tumour encapsulation, in which a fibrous capsule develops around the

tumour, and vascular invasion, in which the malignancy spreads into the portal or hepatic veins, are important tumour characteristics. Encapsulated HCCs appear to be less aggressively invasive than tumours without this feature.<sup>129</sup> Vascular invasion is valued as an early indicator of the aggressiveness of a tumour (for example, its metastatic potential or the likelihood of rapid recurrence following treatment).<sup>130</sup> Rates of vascular invasion are significantly lower in tumours that are small,<sup>131</sup> histologically well differentiated<sup>132</sup> or encapsulated.<sup>129</sup> It has also been found that tumours arising in women are more likely to be encapsulated<sup>133</sup> and less likely to show vascular invasion.<sup>133,134</sup>

## Staging systems

Various staging systems seek to provide prognostic information by combining data about tumour characteristics, underlying liver function and/or patient condition; these have been reviewed in detail elsewhere.<sup>135–137</sup> In Western populations, the most widely used systems are as follows:

- The **TNM** (tumour node metastasis) system ranges from I (early cancer with good prognosis) to IV-B (very advanced HCC with extremely poor prognosis). It is commonly used to summarise tumour-related factors, but is unable to account for the patient’s liver function or clinical condition.

- The **Okuda** score was proposed in 1985. It combines a simple index of tumour extensiveness with information about liver function. However, because it is unable to distinguish between tumours on anything but the crudest level, it is generally considered out of date, in the context of modern diagnostic and therapeutic techniques.<sup>138</sup>
- The **CLIP** (Cancer of the Liver Italian Program) system is a composite score, categorising patients on the basis of broad-gauge measures of liver function (Child–Pugh status) and tumour morphology (three-way index of size and multinodularity), to which are added two prognostically significant dichotomised variables: substantially elevated AFP level and presence of portal vein thrombosis. A total score of 0–6 is produced. Like the Okuda score, the CLIP score cannot distinguish between apparently disparate tumour types, but its predictive power has been validated in a variety of settings.<sup>139–141</sup>
- The **BCLC** (Barcelona Clinic Liver Cancer) staging system divides cases into early, intermediate, advanced and end-stage categories, and is the basis of the Barcelona unit's treatment algorithm. Several tumour-related variables (size, multinodularity, presence of vascular invasion and extrahepatic spread) are taken into account, as are the patient's Child–Pugh score and performance status.

None of these systems has gained unanimous acceptance, although elements of each have been found pragmatically useful by various investigators. It has been argued that the geographical differences in disease profile are such that a single, universal staging system may be an unrealistic target.<sup>135</sup>

### Natural history

The true natural history of HCC is impossible to characterise fully. In the past, patients only presented at an advanced, symptomatic phase of disease. Following advances in diagnostic methods, cases can be detected at an earlier stage, but this progress has been accompanied by the development of therapeutic techniques, the active objective of which is to disrupt underlying prognosis.<sup>135</sup>

Unless detected early, HCC carries a dismal prognosis. It is commonly asserted that patients who present with advanced, untreatable HCC have a median survival of less than 6 months.<sup>135,142</sup> Llovet and colleagues amalgamated results from the control arms of two RCTs at their unit, calculating that a subgroup of patients with advanced, symptomatic HCC survived for a

median of 5.4 months after diagnosis.<sup>143</sup> This finding accords well with several other studies which suggest that patients who receive supportive care alone have a median survival in the range 3–7 months.<sup>83,137,144–146</sup>

However, these figures are likely to be affected by selection bias. For example, patients may be more likely to receive no active treatment if they present with the kind of advanced, symptomatic tumour that places them at the gloomier end of the prognostic spectrum.

According to US registry data from 1992 to 1996, median survival for all patients with HCC regardless of treatment was 0.64 years (1- and 5-year relative survival rates of 23% and 6%).<sup>147</sup> There are no analogous data for the UK, although 1- and 5-year survival rates for all PLC in England were 11% and 3%, respectively, in 1985–1989.<sup>148</sup>

Several pathological features have prognostic significance. Tumours with well-differentiated histology are associated with better survival.<sup>128</sup> Encapsulated tumours show longer disease-free and overall survival, although the thickness of the capsule does not appear to be significant.<sup>129</sup> Absence of vascular invasion (gross or microscopic) is a highly significant indication of better prognosis.<sup>149,150</sup>

## Treatment for hepatocellular carcinoma

### Resection

Surgical resection of the tumorous liver (hepatectomy) is the simplest curative therapy for HCC. A variety of conceptual and technical advances, starting with the development of segmental anatomical principles in the 1950s, has made the approach progressively safer and more effective.<sup>151</sup>

### Indications

According to guidelines published by the British Society of Gastroenterology<sup>96</sup> and the European Association for the Study of the Liver,<sup>152</sup> patients with single tumours less than 5 cm in diameter or three nodules smaller than 3 cm in diameter can be considered for resection (although additional research has shown that patients with larger tumours may also benefit.<sup>153–157</sup>).

The efficacy of resection is predominantly dependent on the functional viability of the non-tumorous liver and, as a result, the best results are

achieved when removing carcinomas from non-cirrhotic livers.<sup>158,159</sup> At the other end of the spectrum, cirrhotic decompensation of Child–Pugh grade B or C is considered an absolute contraindication to resection.<sup>96,152</sup>

## Results

### Perioperative mortality

Song and co-workers reviewed published surgical series from various countries, concluding that, following a substantial improvement in results over the past two decades, most major centres are now achieving perioperative mortality rates of 5% or less.<sup>160</sup> Some Far Eastern units have now reported lengthy series (>100 consecutive patients) without any perioperative deaths.<sup>161–163</sup> Patients are more susceptible to postoperative liver failure when resection leaves them with only a small volume of remnant liver.<sup>164</sup>

### Long-term survival

Song and colleagues' review suggests that, over the past 20 years, 5-year survival following resection has been in the range 30–50%.<sup>160</sup> This estimate is derived from a sample of publications that is dominated by series from the Far East, where patients may have better prognosis owing to lower age and higher rates of patients without cirrhosis. Nevertheless, it seems broadly in line with estimates from exclusively Western populations. In an analysis of a US epidemiological database, patients who were recorded as undergoing resection of their HCC had a 1-year survival of 72.7% and a 5-year survival of 32.5% (compared with 40.9% and 7.3%, respectively, for patients who did not have surgery).<sup>165</sup> Recent reviews from the Barcelona group have asserted that, with meticulous selection of optimal candidates, a 5-year survival rate of 70% can be achieved.<sup>73,152</sup> Vascular invasion is an important predictor of outcome, with an almost two-fold risk of cancer-related death in patients with vascular invasion.<sup>166</sup>

### Disease recurrence

The most common cause of death in patients who have undergone resection is recurrent intrahepatic tumour.<sup>167</sup> Early recurrence (<1 year) is thought to develop from residual cancerous material,<sup>160</sup> and tends to be predicted by tumour-related factors (large, multifocal and/or vascularly invasive tumours are associated with increased risk<sup>168,169</sup>). In contrast, late-recurring HCCs (>5 years after resection) are considered to be new primary tumours. Occurrence is largely dependent on the malignant potential of the underlying liver disease and, as such, indices of liver function provide the most useful prognostic information.<sup>170</sup>

In cohorts consisting partially or wholly of patients with cirrhosis, disease recurs within 5 years in 50–65% of surviving patients.<sup>171–175</sup> Published disease-free survival rates (i.e. the cumulative probability of avoiding both death and disease recurrence) predominantly fall within the following ranges: 50–80% at 1 year, 30–50% at 3 years, 15–40% at 5 years and 8–20% at 10 years.<sup>158,166,173,174,176–193</sup>

## Transplantation

Because orthotopic liver transplantation (OLT) seeks to address not only HCC but also underlying liver disease, it is theoretically superior to resection. Since the first procedure in 1968, over 10,000 OLTs have been performed in the UK (UK Transplant website: <http://www.uktransplant.org.uk>). HCC was listed as a primary or subsidiary diagnosis in 281 (13.7%) of the 2029 first adult elective OLT undertaken in the UK between 1 January 1996 and 31 December 2004 (data provided by UK Transplant).

### Indications

The early history of OLT for HCC was characterised by high recurrence rates and disappointing survival, but results began to improve markedly when stringent selection criteria were applied to prospective candidates.<sup>96,142</sup> The most widely adopted criteria were those published by the Milan unit in 1996, which stipulate that candidates should be considered for OLT if they have either a solitary tumour no more than 5 cm in diameter, or multicentric HCC with up to three nodules, so long as none exceeds 3 cm in diameter.<sup>194</sup> More recently, the team from University of California, San Francisco, has argued that the Milan criteria can be “modestly expanded” to include solitary tumours 6.5 cm in diameter or smaller, and multicentric tumours with up to three nodules 4.5 cm or smaller, and aggregate tumour diameter 8 cm or less.<sup>195</sup>

Malignant invasion of the venous drainage, which is strongly associated with tumour recurrence following OLT (see below), is also considered a contraindication.<sup>196</sup> However, while macrovascular invasion may be detected on preoperative imaging, microvascular infiltration is a histopathological diagnosis that, in the absence of preoperative biopsy, cannot be made prior to hepatectomy.<sup>197</sup> Extrahepatic metastases also contraindicate OLT.<sup>196</sup>

NHS guidance stipulates that patients should be listed for OLT “only if the clinician feels that they have a greater than 50% probability of survival at

5 years after transplantation with a quality of life that is acceptable to the patient.”<sup>198</sup>

## Results

### Perioperative mortality

Although one Chinese unit has recently reported a series of 67 consecutive procedures without any deaths,<sup>199</sup> it is generally accepted that early mortality rates for OLT are likely to exceed those for resection.<sup>200</sup> Published series from the past two decades tend to provide perioperative mortality rates of under 15%, with the most recent predominantly falling in the range 2–8%.<sup>193,194,199,201–213</sup> One UK unit has reported that, during their experience with OLT for small HCC from 1995 to 1999, there were four perioperative mortalities in 30 cases (13.3%).<sup>214</sup>

### Long-term survival

Having adopted the narrow selection criteria described above, several units have been able to achieve a 5-year survival rate of 70–75%.<sup>194,212,215,216</sup> These results are commonly cited in contemporary reviews and guidelines,<sup>152,217</sup> although US registry evidence suggests that 60% may be a more realistic figure.<sup>218</sup> There is some evidence that HCV-related cases may be associated with poorer survival.<sup>217</sup>

### Disease recurrence

When performed in cases meeting current selection criteria, OLT prevents early disease recurrence in the majority of cases; it is commonly asserted that 5-year recurrence rates of no more than 25% are achievable.<sup>142,152</sup> Where vascular invasion is undetected preoperatively (or is not considered an exclusion criterion), it is associated with starkly increased recurrence rates.<sup>150,171,219</sup>

### Graft reinfection

Where OLT is undertaken for HCC secondary to viral hepatitis, there is a significant risk that the implanted liver will become infected. In HCV, graft reinfection is an invariable finding, and the patient is classified as cirrhotic within 5 years in 10–30% of cases.<sup>220–222</sup> In HBV, immunoprophylactic and/or antiviral therapy provides relatively effective protection against graft reinfection, although such treatment is expensive.<sup>223</sup>

### Availability and allocation of donor organs; the waiting list

OLT is only a viable therapy if sufficient cadaveric livers are available for implantation. In the UK, donor livers are allocated according to a national sharing scheme, with priority given to the most urgent cases.<sup>224</sup> It has recently been asserted that most UK patients requiring OLT receive treatment

“without major delay.”<sup>96</sup> In the most recent published UK cohort of patients undergoing OLT for HCC (1995–1999), median time on the waiting list was 36 days (range 1–370 days).<sup>214</sup> However, it appears that waiting times may be getting longer: at present, adults in the UK wait a median of 73 days for a suitable liver.<sup>225</sup> In March 2005, there were 271 patients on the transplantation list.<sup>226</sup>

In the USA, organ allocation is prioritised according to the Model for End-stage Liver Disease (MELD) score, a composite measure based on three biochemical variables – serum bilirubin, creatinine levels and the international ratio of prothrombin time – which has been shown to correlate accurately with the probability of survival on the waiting list.<sup>227</sup> We understand from our expert advisory group that some individual UK units are adopting this method of according priority to patients awaiting OLT.

Inevitably, tumours will continue to progress while patients await OLT, in some cases to an extent that contraindicates OLT. In one US study, 6- and 12-month dropout rates of 7.3% and 25.3%, respectively, were recorded. In Barcelona, they were 11% and 38%, respectively.<sup>216</sup>

Of the 1088 patients on the UK OLT waiting list in 2004/5, there was an 8% dropout rate and an additional 7% of patients died. These figures include all patients on the waiting list for a liver transplant, not only those whose primary indication was HCC.<sup>226</sup>

As discussed below, it is possible that suitability for OLT may be preserved by adjuvant treatment on the waiting list.<sup>228</sup>

### Other interventions

A wide armamentarium of further treatments for HCC is available, as an alternative or a supplement to resection/OLT:

- In **percutaneous ethanol injection (PEI)**, absolute alcohol is injected into the HCC(s) under computed tomography (CT) or ultrasound guidance. The procedure is considered to be simple, inexpensive and relatively safe.<sup>229</sup> The majority of smaller tumours can be totally ablated, excellent 1-year survival rates (90% or better) can be achieved, and some long-term results are only slightly inferior to those achieved with resection (5-year survival of around 40–50%).<sup>230–233</sup>
- Of several thermal ablation techniques, the most commonly used is **radiofrequency**

**thermal ablation** (RFA), in which tumour temperature is raised via a needle electrode, causing necrosis of the tissue. RFA can be performed during open surgery or laparoscopically, but is most commonly performed percutaneously, with ultrasonographic image guidance. Two recent randomised controlled trials (RCTs) have suggested that the short-term results of RFA may be slightly superior to those of PEI; however, no long-term follow-up is reported.<sup>234,235</sup> The UK National Institute for Health and Clinical Excellence (NICE) has published guidance stipulating that RFA should always be monitored using ultrasound or CT, and should only be used following consideration, in each individual case, by a multidisciplinary team including a surgeon.<sup>236</sup>

- **Transarterial chemoembolisation (TACE)** combines embolic obstruction of the tumour's arterial supply (leading to ischaemic necrosis) with localised delivery of a chemotherapeutic agent (often doxorubicin or cisplatin). A meta-analysis of seven RCTs comparing TACE with conservative management showed a significant benefit in terms of 2-year survival rates (41% vs 27%; odds ratio 0.53, 95% CI 0.32 to 0.89;  $p < 0.017$ ).<sup>237</sup> However, it is recognised that TACE is susceptible to several potentially serious complications, including toxic and/or ischaemic damage to the functional liver.<sup>238</sup> There is also an appreciable procedure-related mortality (approximately 4%, rising to 10–20% in decompensated patients).<sup>239</sup>
- Several types of intravenous **chemotherapy** have been investigated. None shows clear evidence of effectiveness, and none is recommended for routine practice at present.<sup>96,152</sup> Similarly, antioestrogen therapy, most commonly with **tamoxifen**, is not associated with a treatment effect in high-quality trials.<sup>237</sup>

### Choice of treatment

Although resection and OLT are the preferred treatment options, only a small proportion of cases are suitable for these approaches. The Barcelona team suggests that only 5–10% of the HCC patients they see can be resected.<sup>240</sup> In The Netherlands in 1989–1998, 12% of the registered HCC cases underwent resection or OLT.<sup>241</sup> Similarly, analysis of a US database showed that 10.4% of the total HCC population in 1988–1998 underwent resection.<sup>165</sup>

There are a few groups of patients for whom resection is preferred to OLT or vice versa.

Resection is the primary therapy for HCC in non-cirrhotic livers,<sup>96</sup> owing to excellent survival rates (see above), coupled with some disappointing experience in OLT for this indication.<sup>242</sup> Conversely, resection is contraindicated in patients with HCC arising in decompensated cirrhosis (see above), so OLT is the only viable curative treatment.

Patients with small HCCs arising in compensated cirrhosis are suitable for either approach. The long-term freedom from recurrence achievable with OLT probably makes it the treatment of choice,<sup>96</sup> although this presumes that organ availability will not compromise the effectiveness of the programme. The Barcelona clinic's experience suggests that average waiting time should be maintained at less than 6 months. Above this cut-off, waiting list dropout will have a negative impact on survival rates, making OLT inferior to resection, when compared on an intention-to-treat (ITT) basis.<sup>216</sup>

The European Association for the Study of the Liver (EASL) guidelines summarise current best practice by suggesting that each decision should be made individually, with a view to locally available resources “in terms of technical skills, experience and organ availability.”<sup>152</sup>

Non-surgical interventions are used in a variety of situations. According to current UK guidelines, they should only be used where resection is contraindicated.<sup>96</sup> Nevertheless, at least one British author has suggested that, as the evidence base evolves, one or more novel techniques may prove to be comparable with resection in terms of crude survival advantage and, in the long run, discrimination between the available treatments may be dominated by questions of cost, safety and quality of life.<sup>243</sup>

Increasingly, techniques such as those described above are being used with the aim of delaying tumour progression in patients awaiting OLT (neoadjuvant or bridging therapy).<sup>244</sup> This approach has not been assessed in any randomised trials; however, some observational<sup>245–248</sup> and modelling<sup>228,249</sup> studies have suggested that it may assist in waiting list management, thereby maximising the effectiveness of an OLT programme. It has been emphasised that, although bridging strategies may induce objectively demonstrable pretransplant tumour control, this apparent effectiveness may not ultimately be reflected in survival benefit following OLT.<sup>250</sup>



## Screening for and diagnosis of hepatocellular carcinoma

### Diagnostic tests

#### Serum AFP testing

AFP is present in high concentrations in fetal blood serum but, soon after birth, it drops to much lower levels. AFP is produced by immature hepatocytes and can therefore be seen at times of liver regeneration (i.e. in active disease with ongoing liver repair) or with some hepatocellular tumours that are made up of transformed, often immature hepatocytes. Elevated levels of AFP are therefore frequently detectable in patients with liver disease, particularly HCC, and consequently, serum AFP assay has been used as a cheap, simple screening method for HCC for many years.

Unfortunately, the sensitivity of AFP as a diagnostic tool is substantially restricted by the existence of non-secreting tumours. The consensus is that up to 20% of HCCs do not produce elevated levels of AFP.<sup>96</sup> It has been suggested that non-AFP-secreting tumours may arise more frequently in alcohol-related cirrhosis.<sup>251</sup> What is more, the test's specificity is limited by the known incidence of raised AFP in non-malignant liver disease: transient or sustained increases of AFP may occur in the absence of HCC, especially in patients experiencing inflammatory flares of chronic viral hepatitis.<sup>152</sup>

As a result of these factors, the diagnostic effectiveness of AFP depends on the chosen cut-off value. Several cut-off values have been investigated, but the broadest range of literature relates to a watershed of 20 ng/ml. Daniele and colleagues summarise seven studies in which this cut-off was adopted, reporting a sensitivity ranging between 41 and 65% and a specificity of 80–94%. Predictably, the use of higher cut-off levels results in increased specificity, but at significant cost to the test's sensitivity.<sup>252</sup>

Because AFP assay apparently has relatively poor sensitivity at any cut-off level, it is increasingly argued that it is an inadequate screening test when used on its own.<sup>253</sup> One editorial goes as far as to announce its "Obituary".<sup>254</sup> It has been suggested that AFP assay is still useful in confirming suspicions raised in imaging studies,<sup>254</sup> or that it might function effectively as a form of triage, with elevated AFP (and/or increasing levels over a series of periodic measurements) used to identify patients in whom detailed, sensitive investigation should be an urgent priority.<sup>152</sup>

### Ultrasonography

Ultrasonography has been a universal choice for first-line imaging of the liver since the 1980s. It is widely available and very efficient, especially when compared to more detailed but more expensive, unwieldy imaging technologies, such as magnetic resonance imaging (MRI) and CT. The reliability of ultrasonographic diagnosis of HCC is variable and depends on a range of factors, including the expertise of the operator and the sophistication of the equipment.

The reported sensitivity of ultrasonography varies as widely as 35–84%.<sup>255</sup> However, the reference standards used in these series are variable and, in some cases, of limited validity (for example, biopsy may confirm suspected cases, but this method will not adequately detect false-negative findings). When measured against the reference standard of explant pathology in transplantation series, the proportion of patients with HCC who are correctly identified by ultrasound is between one-third and two-thirds. False-positive results are less pervasive: the same studies report specificities in the range 92–98%.<sup>256–262</sup>

There is good evidence that larger lesions are more reliably identified on ultrasonography. In Bennett and co-workers' study, sensitivities for the detection of HCCs of diameter greater than 5 cm, 3–5 cm, 2–3 cm, 1–2 cm and less than 1 cm were 75%, 50%, 20%, 13.6% and 0%, respectively.<sup>256</sup> Other teams have found a similar correlation between tumour size and ultrasound sensitivity.<sup>258,259,261</sup>

The technology of ultrasound diagnosis is evolving rapidly; it is anticipated that advances such as microbubble contrast enhancement and harmonic imaging techniques will significantly improve early detection rates in coming years.<sup>263–266</sup> There is also a possibility that these developments will raise false-positive findings.

### Other tests

In addition to AFP, several other serological markers of HCC have been studied, most notably des-gamma carboxyprothrombin (DCP). However, assays of such markers are not routine in clinical practice.<sup>267</sup>

The other radiographical tests that are commonly used in the diagnosis of HCC are CT and MRI. When measured against the optimal reference standard of explant pathology in transplantation series, CT has a sensitivity in the range 44–68%.<sup>268</sup> In a 1997 UK study of iodised oil CT, 44% of HCCs at least 1 cm in diameter were identified.<sup>269</sup>

MRI has a reported sensitivity in the range 55–77% in similar evaluations.<sup>270</sup> In Europe, CT and MRI are generally considered too expensive and inconvenient to be used in primary screening;<sup>152</sup> in contrast, a 1998 survey of US specialists showed that one-quarter used CT for this purpose.<sup>271</sup>

Biopsy is contraindicated in cases of potential HCC, owing to the risk of tumour ‘seeding’ (dissemination of malignancy when tumour cells leak along the track created by the biopsy needle), which may occur in up to 5% of cases.<sup>272</sup> UK guidelines stipulate that biopsy should be avoided where possible and, in any event, reserved for cases “where considerable doubt exists”.<sup>96</sup> When used, it is still subject to a significant false-negative rate, since well-differentiated tumour cells can be difficult to distinguish from benign growth.<sup>272,273</sup>

### Surveillance programmes

Routine periodical screening of individuals with cirrhosis is recommended by UK<sup>96</sup> and European<sup>152</sup> guidelines. Further, although we have not ‘audited’ the surveillance of people with cirrhosis for HCC against NHS National Screening Committee criteria,<sup>274</sup> other recent reviews report that most of the usual recognised criteria for defining what constitutes a viable and effective screening programme are met (with the main exception being a total lack of high-quality RCTs).<sup>275,276</sup>

A 2002 survey confirmed that approximately three-quarters of UK gastroenterologists undertake a formal programme of surveillance for HCC in cirrhosis, mostly using a combination of ultrasound and AFP.<sup>277</sup> Similar findings were reported in an analogous US study of 1998.<sup>271</sup>

### Testing and recall pathways

It is a prerequisite of any surveillance programme that there should be a predefined algorithm, prescribing the order in which tests should be undertaken and the basis on which definitive diagnosis may be reached.

European guidelines,<sup>152</sup> which have been modified in practice by the Barcelona group,<sup>97</sup> envisage 6-monthly ultrasound as the primary screening test. When suspicious lesions are identified, subsequent steps depend on the diameter of the abnormality:

- **<1 cm:** Possible HCC. Repeat ultrasound at 3-monthly intervals; if nodule grows, follow further steps as below.

- **1–2 cm:** Probable HCC. Detailed diagnostic work-up indicated (AFP; additional imaging), but definitive diagnosis requires biopsy.
- **2–3 cm:** Highly probable HCC. If ultrasound appearances are characteristic, diagnosis may be established non-invasively, by either confirmatory imaging (CT, MRI, angiography) or AFP > 400 ng/ml. Otherwise, biopsy is necessary.
- **>3 cm:** Almost certain HCC. Approach as per 2–3-cm tumours, but an additional careful search for vascular invasion is indicated.

In practice, biopsy is often not performed, regardless of tumour size, owing to concerns over needle track seeding. Guidelines issued by the American Association for the Study of Liver Diseases (AASLD) in November 2005<sup>253</sup> seek to make this more explicit, with biopsy only recommended for investigation of nodules with atypical vascular patterns.

### Frequency of tests

The optimal frequency of screening has not been established. Lai and colleagues’ audit revealed a wide range of test intervals in use in the UK: some consultants prefer screening to be repeated as frequently as 3-monthly, while others are content to review those at risk once every 2 years.<sup>277</sup>

A screening interval of 6 months is now recommended in UK<sup>96</sup> and European<sup>152</sup> guidelines, on the basis of available evidence as to the growth rate of small tumours. It has been reported that annual screening is not significantly less effective, although the study in question showed a trend towards better results with 6-monthly testing.<sup>278</sup>

An alternative approach is to use AFP assay to define the frequency of ultrasound screening. For instance, Belgian guidelines recommend that ultrasonography should be performed every 6 months in patients with normal AFP, but twice as often in those whose AFP exceeds 20 ng/ml.<sup>279</sup>

### Compliance with surveillance programmes

For a surveillance programme to achieve optimal results, subjects must be willing to attend for screening when required. The available evidence suggests that compliance rates are relatively good in surveillance for HCC: Collier and Sherman’s review of the literature found that between 3 and 18% of at-risk patients with cirrhosis fail to comply with screening programmes.<sup>280</sup> One exception

may be patients with drink-related cirrhosis who remain alcohol dependent (in Belgium, for example, guidelines stipulate that alcoholics who continue to drink should be excluded from surveillance<sup>279</sup>).

### Effectiveness of surveillance

As described above, surveillance for HCC is now a matter of routine practice in the UK and elsewhere. Accordingly, the kind of randomised evidence that would be necessary to demonstrate its effectiveness is extremely unlikely to be generated. Two Chinese RCTs have addressed similar issues in a different population (HBV-positive patients with or without cirrhosis), with conflicting results. Whereas Zhang and co-workers concluded that surveillance

reduced mortality,<sup>281</sup> Chen and colleagues felt that, although the programme had increased detection rates, no positive survival benefit accrued as a consequence.<sup>282</sup>

Although there is no relevant randomised evidence on the subject, several observational studies have investigated the efficacy of surveillance for HCC. The design of these studies is summarised in *Table 2* (case series) and *Table 3* (cohort studies).

The detection of presymptomatic disease should lead to therapeutic advantages compared with the treatment of cases as and when symptoms arise. Studies of surveillance for HCC tend to concentrate on outcomes such as the number and size of

**TABLE 2** Observational studies of surveillance for HCC using AFP and ultrasound: design of prospective case series

Study	Country	Population	Exclusion criteria	Surveillance programme			
				Dates	Freq. (months)	n	Duration (months), mean $\pm$ SD (range)
Benvegnù <i>et al.</i> , 1994 <sup>283</sup>	Italy	Mixed	None	1986–1993	6	290	46.3 $\pm$ 21.4 (8–96)
Borzio <i>et al.</i> , 1995 <sup>284</sup>	Italy	Mixed	C-P C; age >70	1985–1986	6	307	46 $\pm$ 23 (12–95)
Chiaramonte <i>et al.</i> , 1999 <sup>285</sup>	Italy	HBV/HCV	C-P B/C	1981–1993	6	259	64.5 (12–175)
Colombo <i>et al.</i> , 1991 <sup>286</sup>	Italy	Mixed	C-P C; age <35	1985–1986	3–12	417	33 <sup>a</sup> (1–48)
Cottone <i>et al.</i> , 1994 <sup>287</sup>	Italy	Mixed	C-P B/C	1979–1984	6	147	65 (12–96)
Fasani <i>et al.</i> , 1999 <sup>288</sup>	Italy	Mixed	C-P C	1985–	6–12	1,584	NR
Henrion <i>et al.</i> , 2000 <sup>22</sup>	Belgium	Mixed	None	1995	3–6	141	34 <sup>a</sup> (3–42)
Imberti <i>et al.</i> , 1993 <sup>289</sup>	Italy	Mixed	C-P C	1984–1991	3–6	200	44 (6–96)
Izzo <i>et al.</i> , 1998 <sup>290</sup>	Italy	HBV/HCV <sup>b</sup>	C-P B/C	1993–1996	3	1,125	NR
Oka <i>et al.</i> , 1990 <sup>10</sup>	Japan	Mixed	None	1983–1988	2–3	140	41.1 (2–72)
Pateron <i>et al.</i> , 1994 <sup>6</sup>	France	Mixed	C-P C; AFP >15 ng/dl	1986–1987	6	118	35.8 $\pm$ 15 (4–48)
Sangiovanni <i>et al.</i> , 2004 <sup>291</sup>	Italy	Mixed	C-P C	1985–1986	6–12	417	148 (1–213)
Tong <i>et al.</i> , 2001 <sup>292</sup>	USA	HBV/HCV <sup>b</sup>	None	1991–1998	6–12	602	34.5 $\pm$ 24.5 (12–103)
Velazquez <i>et al.</i> , 2003 <sup>8</sup>	Spain	Mixed	Age <40/>65; C-P C	1992–1999	3–6	463	38.6 $\pm$ 25.2 (1–96)
Zoli <i>et al.</i> , 1996 <sup>293</sup>	Italy	Mixed	None	1989–1991	6	164	(7–77)

C-P, Child–Pugh score; Freq., frequency of screening; NR, not reported.  
<sup>a</sup> Median.  
<sup>b</sup> Including patients with precirrhotic chronic hepatitis.

**TABLE 3** Observational studies of surveillance for HCC using AFP and ultrasound: design of cohort studies

Study	Country	Population (P/R)	Exclusion criteria	Surveillance programme			
				Dates	Freq. (months)	n	Duration (months), mean ± SD (range)
Bolondi <i>et al.</i> , 2001 <sup>68</sup>	Italy	Mixed (P)	Age >60, C-P C; AFP >200 ng/dl	1989–1991	6	313	56 ± 31 (6–100)
Dohmen <i>et al.</i> , 2000 <sup>294</sup>	Japan	Mixed <sup>a</sup> (R)	NR	1989–1998	1–4	NR	NR
Giannini <i>et al.</i> , 2000 <sup>295</sup>	Italy	HCV (R)	NR	1993–1998	6	NR	NR
Henrion <i>et al.</i> , 2003 <sup>296</sup>	Belgium	Mixed (P)	None	1995–1998	3–6	293	60 (30–78)
Kemp <i>et al.</i> , 2005 <sup>297</sup>	Australia	Mixed (P)	None	1994–2002	6–12	NR	NR
Solmi <i>et al.</i> , 1996 <sup>298</sup>	Italy	Mixed <sup>b</sup> (P)	None	1988–1998	6	360	56 (18–72)
Tanaka <i>et al.</i> , 1990 <sup>299</sup>	Japan	Mixed <sup>b</sup> (P)	Age >70; Decompensation	1987–1989	3–6	660	NR
Trevisani <i>et al.</i> , 2002 <sup>278</sup>	Italy	Mixed (R)	NR	1988–1998	6/12	NR	NR
Trevisani <i>et al.</i> , 2004 <sup>300</sup>	Italy	Mixed (R)	Age <70 <sup>c</sup>	1988–2001	6/12	NR	NR
Wong <i>et al.</i> , 2000 <sup>301</sup>	USA	Mixed <sup>a</sup> (R)	NR	1993–1998	1–12	NR	NR
Yu <i>et al.</i> , 2004 <sup>302</sup>	Taiwan	Mixed <sup>a</sup> (R)	Age <20/>70	1996–1997	NR	NR	NR
Yuen <i>et al.</i> , 2000 <sup>303</sup>	Hong Kong	Mixed <sup>b</sup> (R)	None	1995–1997	3–6	~2000	NR

P, prospective; R, retrospective.  
<sup>a</sup> Including patients who developed HCC in non-cirrhotic liver.  
<sup>b</sup> Including patients with precirrhotic chronic hepatitis.  
<sup>c</sup> Study explicitly concerned with elderly cohort.

**TABLE 4** Observational studies of surveillance for HCC using AFP and ultrasound: tumour characteristics in case series

Study	HCCs detected	Unifocal (%)	Maximum tumour diameter (cm)				
			Mean ± SD	Median (range)	≤5 (%)	≤3 (%)	≤2 (%)
Borzio <i>et al.</i> , 1995 <sup>284</sup>			2.9 ± 1.0	(1.5–6)			
Colombo <i>et al.</i> , 1991 <sup>286</sup>	26	57.7	6.0 ± 3.7	4.3 (1.5–10)	53.8	34.6	23.1
Cottone <i>et al.</i> , 1994 <sup>287</sup>	30	86.7	2.7 ± 1.1	2.4 (1–5)	86.7	53.3	30.0
Fasani <i>et al.</i> , 1999 <sup>288</sup>	178	72		(0.8–8)		59.0	
Henrion <i>et al.</i> , 2000 <sup>22</sup>	6	100	2.7 ± 0.7	2.5 (2–3.5)	100	66.7	33.3
Imberti <i>et al.</i> , 1993 <sup>289</sup>	38	65.8			47.4	36.8	
Izzo <i>et al.</i> , 1998 <sup>290</sup>	6	100			100	100	
Oka <i>et al.</i> , 1990 <sup>10</sup>	40	85	2.0 ± 1.3	1.7 (0.5–6)	82.5	70.0	62.5
Pateron <i>et al.</i> , 1994 <sup>6</sup>	14	64.3	2.7 ± 0.9	2.5 (1.8–4)	64.3	42.9	28.6
Sangiovanni <i>et al.</i> , 2004 <sup>291</sup>	112	54	3.1	(1.4–8)	37		
Tong <i>et al.</i> , 2001 <sup>292</sup>	31	58.1	3.5	(1.5–6.5)			
Velazquez <i>et al.</i> , 2003 <sup>8</sup>	38	50			39.5		
Zoli <i>et al.</i> , 1996 <sup>293</sup>	34	82.4	1.9 ± 0.9	1.6 (0.8–4)	100	94.1	58.8

tumours detected, in deference to established treatment parameters that suggest that HCCs are best treated when small and uninodular. Where the observational studies identified report such outcomes, their results are tabulated in *Table 4* (case series) and *Table 5* (cohort studies). These data suggest that HCCs detected during formal surveillance programmes are smaller and more likely to be uninodular

than those that present symptomatically or by chance.

Several of the studies also investigated whether this theoretical advantage translated into tangible benefit, by assessing treatability rates and survival in their screened cohorts. These data are tabulated in *Table 6* (case series) and *Table 7* (cohort studies).

**TABLE 5** Observational studies of surveillance for HCC using AFP and ultrasound: tumour characteristics in cohort studies

Study	HCCs detected	Unifocal (%)	Maximum tumour diameter (cm)					
			Mean $\pm$ SD	Median (range)	$\leq 5$ (%)	$\leq 3$ (%)	$\leq 2$ (%)	
<i>Bolondi et al.</i> , 2001 <sup>68</sup>								
Surveillance group	61	80.3	2.7 $\pm$ 1.1		80.3	52.5	24.6	
Unscreened controls	104	52.9	3.3 $\pm$ 3.2					
<i>Dohmen et al.</i> , 2000 <sup>294</sup>								
1-month surveillance group	102	69.6						47.1
Irregular surveillance group	248	44.0						18.5
Unscreened controls	186	31.9						11.8
<i>Giannini et al.</i> , 2000 <sup>295</sup>								
Surveillance group	34	58.8						
Unscreened controls	27	51.9						
<i>Henrion et al.</i> , 2003 <sup>296</sup>								
Surveillance group	17	94.1			94.1	76.5		
Unscreened controls	40				25.0			
<i>Kemp et al.</i> , 2005 <sup>297</sup>								
Surveillance group	41	56.8	3.2					
Unscreened controls	55	45.7	6.0					
<i>Solmi et al.</i> , 1996 <sup>298</sup>								
Surveillance group	24	75				100		
Unscreened controls						15.5		
<i>Tanaka et al.</i> , 1990 <sup>299</sup>								
Surveillance group	22	81.8			[100] <sup>a</sup>	[83.3] <sup>b</sup>	61.1	
Unscreened controls	83	43.4			[69.4] <sup>a</sup>	[52.8] <sup>b</sup>	16.7	
<i>Trevisani et al.</i> , 2002 <sup>278</sup>								
6-month surveillance group	215	56.3			54.4	42.3		
12-month surveillance group	155	54.2			49.7	37.4		
Unscreened controls	451	42.8			27.7	15.7		
<i>Trevisani et al.</i> , 2004 <sup>300</sup>								
Surveillance group	158	62.7		3.0 (2.2–3.3) <sup>c</sup>	60.8	43.0		
Incidentally diagnosed controls	138	48.6		4.0 (3.0–5.0) <sup>c</sup>	35.5	23.9		
Symptom diagnosed controls	67	35.8		4.0 (3.5–5.0) <sup>c</sup>	22.4	6.0		
All unscreened controls	205	44.4			31.2	18.0		
<i>Wong et al.</i> , 2000 <sup>301</sup>								
Surveillance group	16							6.3
Unscreened controls	75							1.3
<i>Yuen et al.</i> , 2000 <sup>303</sup>								
Surveillance group	142	66.9		3.5 (0.5–15)	61.3	40.1		
Unscreened controls	164	58.5		8.1 (1.3–25)	11.6	4.9		
<i>Yu et al.</i> , 2004 <sup>302</sup>								
Surveillance group	164	75.6			84.8			
Unscreened controls	516	55.8			37.2			

<sup>a</sup>  $\leq 6$  cm.  
<sup>b</sup>  $\leq 4$  cm.  
<sup>c</sup> Interquartile range.

Again, it appears that patients whose disease is detected via formal surveillance are more likely to receive curative treatment, compared with those whose diagnosis is symptomatic or incidental. Moreover, it appears as though the screened

patients benefit from increased survival, although it is important to consider the potential for lead-time bias in the measurement of survival-related outcomes of screening programmes. Because survival is measured from the date of diagnosis,

**TABLE 6** Observational studies of surveillance for HCC using AFP and ultrasound: eligibility for treatment and survival in case series

Study	Treatment (%)			Median survival (months)	Actuarial survival rates (%)				
	Any	Resection	OLT		1-year	2-year	3-year	4-year	5-year
Cottone <i>et al.</i> , 1994 <sup>287</sup>	33.3	6.7							
Henrion <i>et al.</i> , 2000 <sup>22</sup>	100	0	0	8					
Imberti <i>et al.</i> , 1993 <sup>289</sup>	23.7	2.6	2.6						
Izzo <i>et al.</i> , 1998 <sup>290</sup>	100	100							
Oka <i>et al.</i> , 1990 <sup>10</sup>	82.5	17.5			72	53	41		
Pateron <i>et al.</i> , 1994 <sup>6</sup>	35.7	7.1		7	21	7			
Sangiovanni <i>et al.</i> , 2004 <sup>291</sup>	61	5	9	23 <sup>a</sup>	69 <sup>a</sup>	49 <sup>a</sup>	38 <sup>a</sup>	28 <sup>a</sup>	18 <sup>a</sup>
Tong <i>et al.</i> , 2001 <sup>292</sup>	67.7	12.9	25.8						
Velazquez <i>et al.</i> , 2003 <sup>8</sup>	71.1	5.3	28.9						
Zoli <i>et al.</i> , 1996 <sup>293</sup>	58.8	5.9							

<sup>a</sup> Estimate derived from published Kaplan–Meier curve (precise figures not specified).

cases that are detected in an early, presymptomatic phase will appear to benefit from increased lifespan, even if the patient's course has been entirely unaffected by the intervention. Accordingly, HCCs detected during surveillance will appear to have longer survival than cases that were first diagnosed later in their clinical progression.

Trevisani and colleagues performed an adjusted analysis of their survival data to account for lead-time bias, in which surveillance remained associated with significantly longer survival.<sup>278</sup> The studies of Kemp and co-workers<sup>297</sup> and Yuen and colleagues<sup>303</sup> also consider lead-time bias and each conclude that it may account for some but not all of the discrepancy observed between screened cases and controls.

### Cost-effectiveness of surveillance

The searches identified six published cost-effectiveness or cost-utility analyses of the surveillance of patients to detect HCC.<sup>304–309</sup> Three were considered to have less relevance to the project scope and policy context of surveillance for HCC in the current NHS.<sup>305,308</sup> One of these, the oldest (published in 1992), is not strictly a cost-effectiveness analysis and was restricted to people with HBV-related cirrhosis.<sup>305</sup> A more recent study, published in 2004, was based on data from a mixed aetiology cohort of Mexican patients of whom only 42% had cirrhosis. Results were reported in terms of the cost per correct diagnosis.<sup>308</sup> The model-based study by Sarasin and colleagues was based on a simulated generic Western population of 10,000 55-year-old men with Child–Pugh class A cirrhosis.<sup>309</sup> Outputs were presented as cost per life-year saved for the policy of AFP with ultrasound surveillance at 6-monthly intervals.

The three remaining studies were full incremental cost-utility analyses of surveillance based on Markov models among patients with HCV-related cirrhosis in the USA.<sup>304,306,307</sup> All were published since 2003 and appear to have been conducted to good modelling standards. The present analysis was compared with these three studies. Compared with no surveillance, the incremental cost-effectiveness of 6-monthly screening with both AFP tests and ultrasound was between US \$24,500<sup>306</sup> and \$46,600<sup>307</sup> per QALY (equivalent to between £18,400 and £37,300, if inflated and converted to 2005 UK pounds).

For a discussion of these findings in comparison to the present study, see p. 112 and Appendix 11.

## Quality of life

### Impact of cirrhosis on quality of life

Factors that may be associated with impaired health-related quality of life (HRQoL) in patients with cirrhosis include chronic viral infection, emotional problems associated with ongoing substance or alcohol abuse, fear of progressive disease and complications, manifestation of disease complications such as ascites and hepatic encephalopathy, and the adverse effects of treatments (e.g. interferon).

Studies using generic instruments such as the Short Form 36 (SF-36; developed to measure the full range of health and well-being) and the Nottingham Health Profile (developed to measure distress) have demonstrated impaired HRQoL.<sup>310–314</sup> The largest study, conducted in Italy among 544 patients with cirrhosis of varying severities and aetiologies, found that severity of

**TABLE 7** Observational studies of surveillance for HCC using AFP and ultrasound: eligibility for treatment and survival in cohort studies

Study	Treatment (%)			Median survival (months)	Actuarial survival rates (%)				
	Any	Resection	OLT		1-year	2-year	3-year	4-year	5-year
Bolondi <i>et al.</i> , 2001 <sup>68</sup>									
Surveillance group	68.9	9	26	30			45		
Unscreened controls	58.6	8	13	15			31.7		
Dohmen <i>et al.</i> , 2000 <sup>294</sup>									
1-month surveillance group					88 <sup>a</sup>	74 <sup>a</sup>	53 <sup>a</sup>	47 <sup>a</sup>	43
Irregular surveillance group					75 <sup>a</sup>	60 <sup>a</sup>	47 <sup>a</sup>	36 <sup>a</sup>	26
Unscreened controls					53 <sup>a</sup>	40 <sup>a</sup>	30 <sup>a</sup>	22 <sup>a</sup>	15
Giannini <i>et al.</i> , 2000 <sup>295</sup>									
Surveillance group	97.1	11.8	2.9	23 ± 13					
Unscreened controls	66.7	7.4	0	15 ± 14					
Henrion <i>et al.</i> , 2003 <sup>296</sup>									
Surveillance group	82.4	17.6	29.4	32 <sup>a</sup>	73 <sup>a</sup>	51 <sup>a</sup>	34 <sup>a</sup>		
Unscreened controls				11 <sup>a</sup>	43 <sup>a</sup>	29 <sup>a</sup>	18 <sup>a</sup>	15 <sup>a</sup>	11 <sup>a</sup>
Kemp <i>et al.</i> , 2005 <sup>297</sup>									
Surveillance group	63.4	11.8 <sup>b</sup>	29	89	62	38			
Unscreened controls	20	6.8 <sup>b</sup>	3.3	33	24	19			
Tanaka <i>et al.</i> , 1990 <sup>299</sup>									
Surveillance group	100	54.5	0						
Unscreened controls	98.8	32.5	0						
Trevisani <i>et al.</i> , 2004 <sup>300</sup>									
Surveillance group	70.9	8.4	0	24 <sup>c</sup>	70 <sup>a</sup>	50 <sup>a</sup>	43 <sup>a</sup>	17 <sup>a</sup>	11 <sup>a</sup>
Incidentally diagnosed controls	56.5	2.9	0	21	67 <sup>a</sup>	40 <sup>a</sup>	23 <sup>a</sup>	14 <sup>a</sup>	9 <sup>a</sup>
Symptom diagnosed controls	29.9	0	0	7	39 <sup>a</sup>	25 <sup>a</sup>	18 <sup>a</sup>	16 <sup>a</sup>	16 <sup>a</sup>
All unscreened controls	47.8	2.0	0						
Trevisani <i>et al.</i> , 2002 <sup>278</sup>									
6-month surveillance group	74.9 <sup>d</sup>	11.6 <sup>d</sup>	3.9 <sup>d</sup>	36	86 <sup>a</sup>	67 <sup>a</sup>	49 <sup>a</sup>	37 <sup>a</sup>	28 <sup>a</sup>
12-month surveillance group				34	81 <sup>a</sup>	67 <sup>a</sup>	46 <sup>a</sup>	33 <sup>a</sup>	19 <sup>a</sup>
Unscreened controls	54.3	8.2	0.2	14	52 <sup>a</sup>	36 <sup>a</sup>	23 <sup>a</sup>	16 <sup>a</sup>	12 <sup>a</sup>
Wong <i>et al.</i> , 2000 <sup>301</sup>									
Surveillance group	100	25	12.5	46	80 <sup>a</sup>	65 <sup>a</sup>	65 <sup>a</sup>	0 <sup>a</sup>	
Unscreened controls	65.3	18.7	1.3	7.7–17.9 <sup>e</sup>	43–60 <sup>a,e</sup>	35–45 <sup>a,e</sup>	17–23 <sup>a,e</sup>	0–23 <sup>a,e</sup>	
Yu <i>et al.</i> , 2004 <sup>302</sup>									
Surveillance group		50.6							
Unscreened controls		29.1							
Yuen <i>et al.</i> , 2000 <sup>303</sup>									
Surveillance group	73.9	26.8		22					
Unscreened controls	40.8	7.9		5					

<sup>a</sup> Estimate derived from published Kaplan–Meier curve.<sup>b</sup> Resection and/or transplantation.<sup>c</sup> Adjusted for estimated lead-time.<sup>d</sup> Combined rates across annual and semiannual surveillance groups.<sup>e</sup> Range for symptomatic and incidental cases.

disease (as measured by Child–Pugh score) was most closely correlated with HRQoL, the effects were greatest in younger patients and underlying aetiology of cirrhosis was unrelated to changes in HRQoL.<sup>310</sup>

### **Impact of HCC on quality of life**

Bianchi and colleagues assessed HRQoL using the SF-36 and Nottingham Health Profile in 101 patients with HCC who had received their diagnosis a median of 10 months earlier (range 0–72 months).<sup>315</sup> Scores for both measures showed significant impairment compared with the normative population. However, when these results were compared with results from a group of matched controls ( $n = 202$ ) with a diagnosis of cirrhosis (matched for gender, age, aetiology, Child–Pugh score, severity of ascites and sleep disturbances) there were few differences. Observed differences were primarily related to the pain domains of both questionnaires and were not related to tumour size.

### **Impact of taking part in a surveillance programme for HCC on quality of life**

The reviewers were unable to locate any studies in which the effects on HRQoL of being involved in a surveillance programme were investigated.

### **Impact of liver transplantation on quality of life**

Two small studies were identified in which the HRQoL of patients with cirrhosis on the waiting list for a liver transplant was assessed.<sup>316,317</sup> None of the subjects was on the waiting list as a result of a diagnosis of HCC. Significant associations were observed between HRQoL (specifically the physical

functioning domain of the SF-36 in one study<sup>316</sup>) and the Child–Pugh score. Aetiology of the underlying liver disease had no effect on the results.

Several studies have assessed the effects of liver transplantation on HRQoL but have not focused specifically on liver transplant as a result of a diagnosis of HCC.<sup>312,318,319</sup> The most comprehensive of these assessed HRQoL using EuroQoL 5 Dimensions (EQ-5D) and SF-36 in all individuals selected to receive treatment as part of the UK NHS liver transplantation programme at each of the six liver transplant units in England and Wales during a 2-year period ( $n = 542$ ).<sup>318</sup> A paired comparison of HRQoL before transplantation and 3 months post-transplantation showed significant improvements in both the SF-36 and EQ-5D. Analysis of all patients who survived until the end of the study showed further improvements on both scales.

### **Impact of liver resection on quality of life**

There is very little published evidence surrounding the effect of liver resection on HRQoL in patients with HCC. We identified one study, from China, in which HRQoL was measured using the FACT-G questionnaire, in 66 consecutive patients undergoing resection for HCC.<sup>320</sup> Significant improvements in HRQoL were seen 3 months postoperatively. A total of 46 patients completed all postoperative assessments (up to 24 months postoperatively); at all time-points their mean scores were higher than those recorded preoperatively. Development of recurrence was the main factor leading to deterioration in HRQoL over time.



# Chapter 2

## Systematic review

### Methods

The review generally adhered to the methodological guidelines published by the NHS Centre for Reviews and Dissemination (York) Report No. 4.<sup>321</sup>

### Inclusion and exclusion criteria

Studies were included or excluded from the review with regard to the criteria listed in *Box 1*. One exclusion criterion (irrelevance to the UK setting) requires qualification. Because the incidence and aetiology of cirrhosis vary widely between the UK and elsewhere (especially the Far East and the developing world; see Chapter 1), studies from Asia and Africa were only considered for inclusion if they contained sufficient detail to enable us to consider the impact of key population differences. In particular, we looked for detailed information about age and co-morbidity, and required separate reporting of findings according to underlying cause of cirrhosis. The situation in Europe and elsewhere in the developed world is considered more relevant to the UK setting; however, studies from these places were only considered for inclusion if they contained sufficient detail to observe and account for any important dissimilarities in the populations.

### Search strategy

Electronic databases were searched for RCTs. Appendix 2 shows the databases searched and the

strategy in full. Bibliographies of articles were also searched.

### Identification of studies

Relevant studies were identified in two stages. Abstracts returned by the search strategy were examined independently by two researchers (JTC and GR) and screened for inclusion or exclusion. Disagreements were resolved by discussion. Full texts of the identified studies were obtained. Two researchers (JTC and GR) examined these independently for inclusion or exclusion and disagreements were resolved by discussion. The process is illustrated in Appendix 3.

### Results

The inclusion/exclusion process is illustrated in Appendix 3.

The searches returned 214 separate references. From screening of abstracts, 207 of these were excluded, leaving seven potentially relevant studies to be reviewed in full. All seven papers were excluded at this stage (see Appendix 4 for a list of these, with reasons for exclusion). Because no studies were identified that met the criteria, we were unable to proceed with the review.

**BOX 1** Inclusion and exclusion criteria for systematic review

	Inclusion	Exclusion
Intervention	<ul style="list-style-type: none"> <li>Surveillance for HCC using AFP and/or ultrasound</li> </ul>	<ul style="list-style-type: none"> <li>Not surveillance for HCC</li> <li>Surveillance other than AFP and/or conventional ultrasound</li> <li>Surveillance for outcomes other than HCC</li> </ul>
Comparators	<ul style="list-style-type: none"> <li>No intervention</li> <li>AFP or ultrasound alone</li> </ul>	
Population	<ul style="list-style-type: none"> <li>Population (total or separately reported) with cirrhosis of known underlying cause (alcohol, HBV or HCV)</li> </ul>	<ul style="list-style-type: none"> <li>Not cirrhotic patients (or mixed population not reported separately)</li> <li>Population with cirrhosis other than alcohol-related, HBV or HCV</li> <li>Not relevant to the UK setting</li> </ul>
Study design	<ul style="list-style-type: none"> <li>RCTs</li> <li>Published in English</li> </ul>	<ul style="list-style-type: none"> <li>Narrative reviews, editorials, letters, case reports and modelling studies</li> <li>Observational (non-randomised) studies, including case series, cross-sectional studies, cohort studies and case-control studies</li> <li>Preclinical or biological studies, animal models</li> <li>Abstract only available</li> <li>Not available in English</li> </ul>



## Chapter 3

# Cost-effectiveness model: methods

### Overview of model

The population of interest is people with a diagnosis of compensated cirrhosis (ALD, HBV and HCV), deemed eligible to enter a surveillance programme; that is, aged 70 years or less with no pre-existing medical conditions that would preclude treatment with liver transplant or hepatic resection (including current alcohol or intravenous drug abuse).

A state transition (Markov) model was constructed using TreeAge Pro™ 2005 (TreeAge Software, Williamstown, MA, USA) to compare various surveillance strategies. Comparisons were made between:

- no surveillance
- annual surveillance using AFP triage
- annual surveillance using ultrasound alone
- annual surveillance using AFP and ultrasound
- 6-monthly surveillance using AFP triage
- 6-monthly surveillance using ultrasound alone, and
- 6-monthly surveillance using AFP and ultrasound.

The technical performance of the alternative testing strategies was modelled using decision trees. Test sensitivity was varied according to tumour size. Expected costs and utilities for each surveillance strategy were calculated using both a cohort and a Monte Carlo simulation approach. The model structure was developed on the basis of literature reviews, in collaboration with the expert advisory group (Appendix 5), and is limited by the availability of reliable and valid parameter estimates against which to calibrate intermediate outputs.

The effectiveness of the various surveillance strategies was estimated by calculating the number of people that would need to be monitored to prevent one death from HCC. The analysis was undertaken from the perspective of the UK NHS. Costs are expressed in UK pounds using 2004 as the base year; estimates from previous years were inflated using published inflation indices for NHS hospital and community health services pay and prices. Benefits and costs were discounted at 3.5%;

other discount rates were explored in sensitivity analyses. Outcomes of the cost–utility analysis are expressed in terms of quality-adjusted life-years (QALYs). The model runs for the lifetime of the population.

### Model structure

The influence diagram is shown in *Figure 3*. States are shown as boxes, logical steps in the transition pathway are shown as ovals and allowable state transitions are shown as arrows. Background mortality (arrows not shown) is also applied to patients in all states of the model. Excess mortality is associated with some states, which are shaded black. There are three parts to the model. The first, the basis of the model, is the disease process or ‘natural history’ component. The surveillance programme and treatment components are then superimposed onto the disease process.

### Simulated populations

The model was developed to allow separate analysis of each of the three cirrhosis aetiologies (ALD, HBV and HCV). Results were also produced for a mixed cohort weighted according to the following proportions: 57.6% ALD, 7.3% HBV and 35.1% HCV (see below).

The starting age (age of diagnosis of cirrhosis) and gender mix of simulated cohorts were based on evidence from appropriate studies in the literature (see below). In the base-case analysis, the surveillance programme was limited to those aged 70 years or less, because the clinical expert advisors suggested that people with cirrhosis older than this would be much less likely to be eligible for curative treatments (e.g. transplantation, liver resection).

### Disease process/natural history

The disease process is time dependent and is represented using a series of disease states, such as compensated and decompensated cirrhosis. Possible movements (transitions) between states

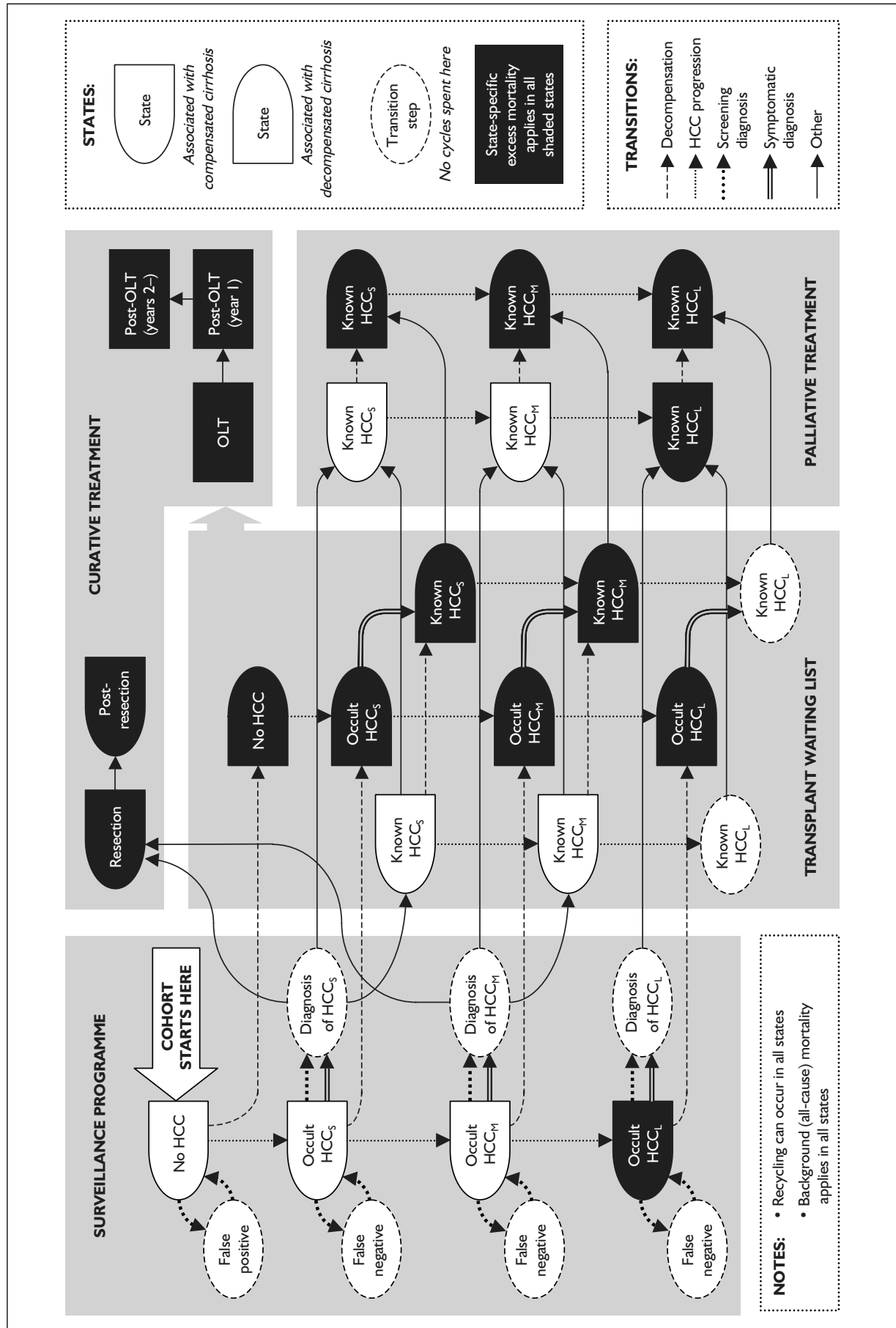


FIGURE 3 Screening for HCC in hepatic cirrhosis: influence diagram. HCC tumours: L, large; M, medium; S, small.

are shown as arrows (see *Figure 4*). Transitions between states occur at fixed time intervals (cycle length). In this model, the cycle length is 1 month; this is short enough to reflect the cost and quality of life impact of major surgical treatment episodes (e.g. transplantation or resection) and to allow the simulation of realistic changes in disease status between surveillance intervals.

A probability is assigned to each of these arrows (transition probability) and governs the likelihood of a person moving from one state to another during a month. Each state also has an associated cost and quality of life (utility). Some transitions also generate costs (e.g. cost associated with surveillance tests). Total costs and utilities are estimated over the lifetime of the simulated population by calculating the amount of time spent in each state (and adding any costs linked to transitions).

Within the natural history model, distinction is made between people with compensated and decompensated cirrhosis. Progression from compensated cirrhosis to decompensated cirrhosis is irreversible. The rate of incidence of HCC is the same in compensated and decompensated livers. HCC can be either be diagnosed or undiagnosed (occult). This distinction allows the model to track the number of people with an unknown HCC tumour who receive a liver transplant for decompensated cirrhosis.

Three classes of HCC tumour were defined. 'Small' tumours are defined as 2 cm or less in diameter, 'medium' tumours as between 2 and 5 cm in diameter, and 'large' tumours as larger than 5 cm in diameter. The model assumes that all tumours are uninodular, and treats diameter as a surrogate measure of all characteristics of tumour progression (there is excellent evidence, for example, that tumour diameter is strongly associated with the probability of vascular invasion<sup>130,131,217</sup>). Therefore, what the model defines as 'medium' tumours would, in real-world practice, include those with multiple, small nodules that would not preclude transplantation, and a 'large' tumour may be thought to include those which are diffuse in nature. Tumour characteristics in terms of detectability and treatability are reflected in the transition probabilities in the surveillance and treatment parts of the model. For example, transition probabilities reflect the assumption that there is a greater likelihood of larger tumours invading the portal vein and becoming symptomatic.

Owing to the lack of evidence surrounding mortality in people with a non-symptomatic tumour, the model assumes that the presence of an HCC tumour has no effect on mortality until it becomes 'large', at which point it becomes very likely to be symptomatic and is associated with an additional mortality rate.

## Surveillance programme

Transition probabilities associated with the surveillance programme are operated at 6- or 12-monthly intervals as appropriate. The technical performance of each testing strategy is modelled using decision trees. Testing strategies (or protocols) were based on European guidelines, which recommend that the diagnosis of HCC be based on findings from two coincident imaging techniques.<sup>152</sup> Two AFP thresholds were used, 20 and 400 ng/ml, as these are associated with the broadest evidence base.

Transition probabilities for the correct and incorrect diagnosis of HCC were calculated using the probabilities associated with the appropriate pathways (see *Table 9*).

In the base-case analysis, the performance of each test is determined only by the presence and size of any HCC tumour. Test performance is independent of the results of previous tests.

As people reach the ceiling age for surveillance (70 years old, in the base case), they leave the surveillance programme and follow a natural history pathway without surveillance.

In the base case, 100% compliance with the surveillance programme was assumed. Other compliance rates have been explored in a scenario analysis. Two types of non-compliance were considered: failure to attend random appointments and dropping out of the programme altogether. The probability that a person is compliant or non-compliant is applied at the same frequency as the testing visits for the appropriate surveillance programme. People who discontinue their participation in the programme follow a natural history pathway without surveillance. Incidental diagnosis is possible from these states.

Incidental/symptomatic presentation of HCC is permitted for people with both compensated and decompensated cirrhosis at all stages of disease (e.g. small, medium and large tumours), although with significantly lower probabilities for those with small or medium-sized tumours.

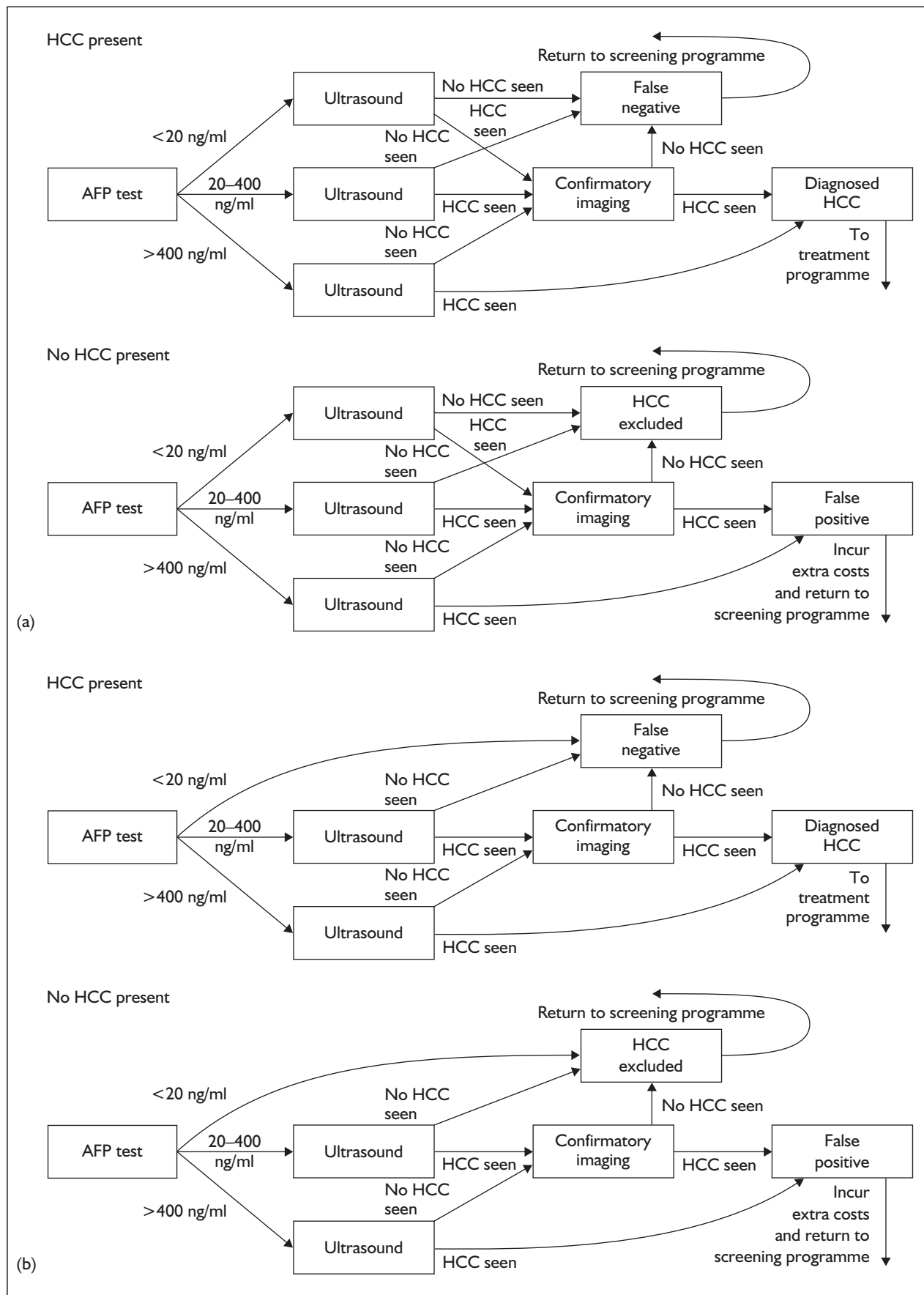
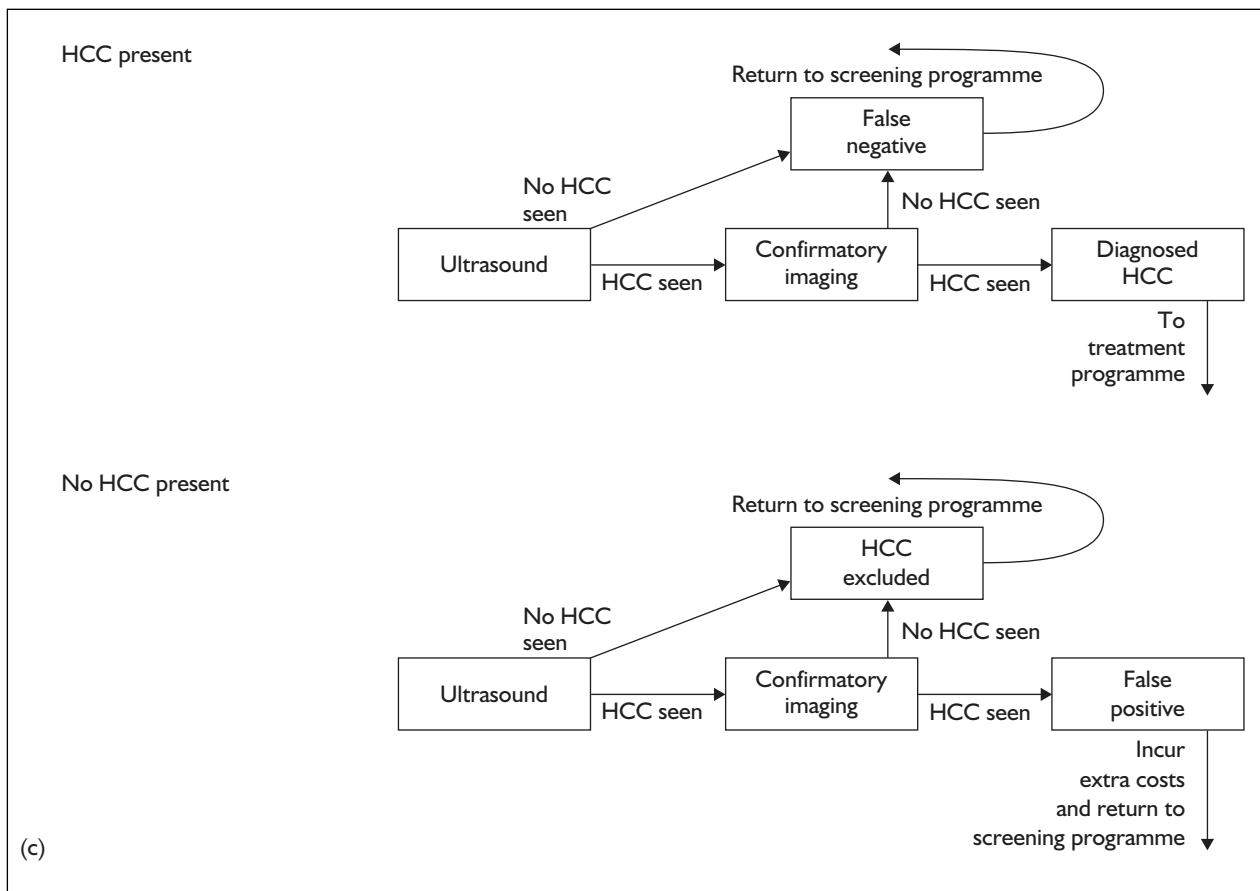


FIGURE 4 Decision trees describing surveillance strategies: (a) AFP and ultrasound; (b) AFP triage; (c) ultrasound



**FIGURE 4 (continued)** Decision trees describing surveillance strategies: (a) AFP and ultrasound; (b) AFP triage; (c) ultrasound

All confirmatory imaging is by CT scan. There is a small rate of false-positive diagnoses as a result of surveillance, all of which are assumed to be rapidly discovered before treatment. This accords with anecdotal evidence from the clinical experts, that on no occasions in their clinical experience had a liver explanted or resected for HCC been found not to contain an HCC tumour. Furthermore, the proportion of modelled false positives was ultimately so small (between 1 in 1000 and 4 in 1000 of those with no HCC tested) as to have no significant effect on model outcomes.

## Treatment

A mixed treatment approach of liver transplantation and resection was modelled. The key structural assumptions used in the model are listed in *Box 2*.

People can enter the transplant waiting list following diagnosis of either surgically treatable HCC or decompensated cirrhosis. There is no

waiting list for liver resection for HCC. Liver resection takes place in the month following diagnosis.

There is no prioritisation of people waiting for a transplant; each person is as likely to receive a liver as any other, regardless of the reason for listing. There is anecdotal evidence that individual UK units prioritise cases using a variety of criteria, with some, but not all, centres relying on MELD score to inform allocation policy, as in the USA (see Chapter 1). Because of this heterogeneity of practice, a decision was made to simplify the model by assuming equal priority for all cases.

During their time on the transplant waiting list, patients are subject to the same natural disease process as those prelisting (i.e. the tumour, if they have one, can progress from small to medium to large; a person with decompensated disease without HCC can develop a tumour that may then progress; and a person with compensated disease and a tumour can become decompensated).

Some people are deemed unsuitable for surgical treatment, including those who are diagnosed with

**BOX 2** Summary of key structural assumptions adopted in model

- All tumours are assumed to be uninodular, with diameter used as a surrogate index of all characteristics of tumour progression.
- Progression from compensated to decompensated cirrhosis is irreversible.
- The rate of incidence of HCC is the same in compensated and decompensated livers.
- The presence of an HCC tumour has no effect on mortality until it becomes 'large', at which point it becomes symptomatic and is associated with an additional mortality rate.
- Test performance is independent of the results of previous tests.
- Incidental/symptomatic diagnosis is possible alongside all interventions, including 'no surveillance'.
- The ceiling age for surveillance is 70 years old.
- In the base case, there is 100% compliance with the surveillance programme.
- All confirmatory imaging is by CT scan.
- There is a small rate of false-positive diagnoses as a result of surveillance, all of which are assumed to be rapidly discovered before treatment.
- There is no waiting list for liver resection.
- There is no prioritisation of people on the transplant waiting list.
- No ablative therapies are applied to patients on the transplant waiting list.
- Some people are deemed to have surgically untreatable tumours at the time of diagnosis of HCC.
- Palliative therapies are administered to some people with untreatable HCC.
- Disease progression and HCC recurrence post-treatment are not modelled as separate health states, but are captured in the mortality rate, costs and disbenefits applied to the post-treatment states.
- There is no post-treatment distinction between people who receive a transplant as a result of decompensation and those that receive a transplant as a result of HCC.

a large tumour and those whose tumour becomes large while on the waiting list. The number of people who receive transplant, resection or who are deemed unsuitable for surgical treatment are based on simple proportions according to tumour size. Small tumours are deemed more amenable to surgical treatment (by both transplant and resection) than medium-sized tumours (see *Table 10*).

People who undergo successful treatment (by either transplantation or resection) enter a simplified disease process in which excess mortality rates and associated costs and utilities encompass the spectrum of possible post-treatment experiences. Separate health states to simulate recurrence of HCC post-OLT have not been developed. However, the parameters used to define patient experience following OLT account for additional mortality risk, utility disbenefit and costs that may be associated with recurrence and further treatment.

People with small and medium-sized tumours that are deemed to be surgically untreatable enter a series of states (palliative care) which mirror the natural history of the disease. Palliative treatments (RFA, PEI, TACE and best supportive care) are applied to some people. The sequence of palliative care was developed with reference to the algorithm proposed by Poon and colleagues.<sup>322</sup>

A proportion of patients with small and medium-sized tumours receive RFA and PEI (see the section 'Surgically untreatable HCC', p. 56). Once people progress to 'terminal HCC large', an excess mortality with associated costs and utilities is applied, which reflects the palliation provided by transarterial chemoembolisation for a fixed proportion of people.

## Parameters

A full list of the parameters used in the Markov model appears in *Tables 8–11*. More detailed descriptions of the sources from which these estimates were obtained and a justification of their choice can be found in Chapter 4.

To derive some of the time-specific parameter values needed for the Markov model from numbers in published research, probabilities were converted to rates using the standard formula:

$$\frac{-\ln(1 - \text{prob})}{\text{time}}$$

Rates were converted to probabilities using the formula:

$$1 - \exp^{-\text{rate} \times \text{time}}$$



**TABLE 8** Parameters used in Markov model: cohort characteristics

Parameter	Cohort	Value	Source	Range of values used in sensitivity analyses	
				Lower	Upper
Mean age of starting cohort (age of diagnosis of cirrhosis)	ALD	53.3	Roberts <i>et al.</i> , 2005 <sup>36</sup>	43.3	63.3
	HBV	44.0	Fattovich <i>et al.</i> , 1995 <sup>98</sup>	34.0	54.0
	HCV	54.0	Fattovich <i>et al.</i> , 1997 <sup>64</sup>	44.0	64.0
Gender mix of cohort (% male)	ALD	70.1%	ONS mortality statistics <sup>a</sup>	50.0%	90.2%
	HBV	86.5%	Fattovich <i>et al.</i> , 1995 <sup>98</sup>	82.6%	89.7%
	HCV	58.1%	Fattovich <i>et al.</i> , 1997 <sup>64</sup>	53.1%	62.9%
Upper age limit for surveillance programmes	All	70	AA	60	80
Composition of mixed aetiology cohort	ALD	57.6%	EO		
	HBV	7.3%			
	HCV	35.1%			

AA, authors' assumption; EO, assumption based on expert opinion.  
<sup>a</sup> Office for National Statistics: *Mortality Statistics: Cause (Series DH2)*. 1999–2003. Available from: [www.statistics.gov.uk/Statbase/Product.asp?vlink=618](http://www.statistics.gov.uk/Statbase/Product.asp?vlink=618)

**TABLE 9** Parameters used in Markov model: values affecting transition probabilities

Parameter	Cohort	Value	Source	Range of values used in sensitivity analyses	
				Lower	Upper
Annual incidence of cirrhosis decompensation	ALD	3.3%	<sup>a</sup>	1.8%	7.0%
	HBV	3.3%	Fattovich <i>et al.</i> , 2002 <sup>67</sup>	1.8%	6.0%
	HCV	5.3%	Fattovich <i>et al.</i> , 2002 <sup>67</sup>	3.9%	7.0%
Annual incidence of HCC	ALD	1.7%	Fattovich <i>et al.</i> , 2004 <sup>323</sup>	1.2%	2.2%
	HBV	2.2%	Fattovich <i>et al.</i> , 2004 <sup>323</sup>	1.6%	2.8%
	HCV	3.7%	Fattovich <i>et al.</i> , 2004 <sup>323</sup>	3.2%	4.2%
Tumour growth rate (volume doubling time)	All	127 days <sup>b</sup>	Taouli <i>et al.</i> , 2005 <sup>324</sup>	80 days <sup>c</sup>	203 days <sup>d</sup>
Probability of AFP ≤20 ng/ml in HCC <sub>S</sub>	All	0.352	<sup>e</sup>	0.261	0.456
Probability of AFP 21–400 ng/ml in HCC <sub>S</sub>	All	0.568	<sup>e</sup>	0.464	0.667
Probability of AFP >400 ng/ml in HCC <sub>S</sub>	All	0.080	<sup>e</sup>	0.039	0.155
Probability of AFP ≤20 ng/ml in HCC <sub>M</sub>	All	0.378	<sup>e</sup>	0.276	0.492
Probability of AFP 21–400 ng/ml in HCC <sub>M</sub>	All	0.500	<sup>e</sup>	0.389	0.611
Probability of AFP >400 ng/ml in HCC <sub>M</sub>	All	0.122	<sup>e</sup>	0.065	0.215
Probability of AFP ≤20 ng/ml in HCC <sub>L</sub>	All	0.222	<sup>e</sup>	0.063	0.547
Probability of AFP 21–400 ng/ml in HCC <sub>L</sub>	All	0.444	<sup>e</sup>	0.189	0.733
Probability of AFP >400 ng/ml in HCC <sub>L</sub>	All	0.334	<sup>e</sup>	0.121	0.646
Probability of AFP ≤20 ng/ml in patients with no HCC	All	0.906	Trevisani <i>et al.</i> , 2001 <sup>251</sup>	0.853	0.941
Probability of AFP 21–400 ng/ml in patients with no HCC	All	0.088	Trevisani <i>et al.</i> , 2001 <sup>251</sup>	0.054	0.140
Probability of AFP >400 ng/ml in patients with no HCC	All	0.006	Trevisani <i>et al.</i> , 2001 <sup>251</sup>	0.001	0.033
Probability of detection of HCC <sub>S</sub> by ultrasound	All	0.107	Bennett <i>et al.</i> , 2002 <sup>256</sup>	0.037	0.272
Probability of detection of HCC <sub>M</sub> by ultrasound	All	0.286	Bennett <i>et al.</i> , 2002 <sup>256</sup>	0.082	0.641

*continued*

**TABLE 9** Parameters used in Markov model: values affecting transition probabilities (cont'd)

Parameter	Cohort	Value	Source	Range of values used in sensitivity analyses	
				Lower	Upper
Probability of detection of HCC <sub>L</sub> by ultrasound	All	0.750	Bennett <i>et al.</i> , 2002 <sup>256</sup>	0.301	0.954
False-positive rate for ultrasound	All	3.5%	Bennett <i>et al.</i> , 2002 <sup>256</sup>	1.6%	7.4%
Probability of detection of HCC <sub>S</sub> by CT	All	1.000	AA	1.000	1.000
Probability of detection of HCC <sub>M</sub> by CT	All	1.000	AA	1.000	1.000
Probability of detection of HCC <sub>L</sub> by CT	All	1.000	AA	1.000	1.000
False-positive rate for CT	All	10.2%	Brancatelli <i>et al.</i> , 2003 <sup>325</sup>	7.6%	13.7%
Annual symptomatic/incidental presentation rate for HCC <sub>S</sub>	All	1.6%	<i>f</i>	0%	16.2%
Annual symptomatic/incidental presentation rate for HCC <sub>M</sub>	All	12.1%	<i>f</i>	0%	30.3%
Annual symptomatic/incidental presentation rate for HCC <sub>L</sub>	All	50.0%	<i>f</i>	0%	100%
Proportion with decompensated cirrhosis who are listed for OLT	All	90%	AA	80%	100%
Proportion with HCC <sub>S</sub> who receive resection	All	20%	AA	10%	30%
Proportion with HCC <sub>S</sub> who are listed for OLT	All	75%	AA	65%	85%
Proportion with HCC <sub>S</sub> who are deemed surgically untreatable	All	5%	AA	5%	5%
Proportion with HCC <sub>M</sub> who receive resection	All	5%	AA	2%	10%
Proportion with HCC <sub>M</sub> who are listed for OLT	All	85%	AA	88%	80%
Proportion with HCC <sub>M</sub> who are deemed surgically untreatable	All	10%	AA	10%	10%
Median wait on OLT waiting list <sup>g</sup>	All	72 days <sup>h</sup>	UKT	68 days <sup>i</sup>	76 days <sup>j</sup>
Annual mortality rate due to compensated cirrhosis	All	0%	AA	0%	5%
Annual mortality rate due to decompensated cirrhosis	ALD	17.7%	<i>k</i>	12.7%	32.5%
	HBV	22.5%	Fattovich <i>et al.</i> , 2002 <sup>67</sup>	18.9%	32.5%
	HCV	12.9%	Fattovich <i>et al.</i> , 1997 <sup>64</sup>	12.7%	14.0%
90-day mortality rate for patients undergoing OLT	ALD	6.0%	UKT	0.0%	12.6%
	HBV	15.0%		4.7%	25.3%
	HCV	7.4%		3.0%	11.8%
Proportion of patients surviving 1 year following OLT	ALD	92.0%	UKT	84.5%	99.5%
	HBV	78.0%		65.9%	90.1%
	HCV	87.6%		81.9%	93.3%
Proportion of patients surviving 5 year following OLT	ALD	54.7%	UKT	38.2%	71.3%
	HBV	68.5%		54.3%	82.8%
	HCV	55.8%		41.0%	70.6%
90-day mortality rate for patients undergoing resection	All	3.9%	Llovet <i>et al.</i> , 1999 <sup>216</sup>	1.3%	10.8%
Proportion of patients surviving 1 year following resection	All	85.0%	Llovet <i>et al.</i> , 1999 <sup>216</sup>	79.0%	88.0%
Proportion of patients surviving 3 year following resection	All	62.0%	Llovet <i>et al.</i> , 1999 <sup>216</sup>	54.0%	76.0%
Proportion of patients surviving 5 year following resection	All	51.0%	Llovet <i>et al.</i> , 1999 <sup>216</sup>	36.0%	58.0%

*continued*

**TABLE 9** Parameters used in Markov model: values affecting transition probabilities (cont'd)

Parameter	Cohort	Value	Source	Range of values used in sensitivity analyses	
				Lower	Upper
Annual mortality rate associated with occult HCC <sub>L</sub>	All	72.9%	Greten <i>et al.</i> , 2005 <sup>83</sup>	34.6%	97.3%
Annual mortality rate associated with known HCC <sub>L</sub>	All	64.4%	<sup>i</sup>	33.6%	84.8%

HCC tumours: S, small ( $\leq 2$  cm); M, medium (2–5 cm); L, large (5 cm); UKT, UK Transplant.

<sup>a</sup> Assumed same as HBV in absence of a reliable ALD-specific estimate.

<sup>b</sup> Monthly probability of progression from HCC<sub>S</sub> to HCC<sub>M</sub> = 0.056; monthly probability of progression from HCC<sub>M</sub> to HCC<sub>L</sub> = 0.036.

<sup>c</sup> Monthly probability of progression from HCC<sub>S</sub> to HCC<sub>M</sub> = 0.036; monthly probability of progression from HCC<sub>M</sub> to HCC<sub>L</sub> = 0.023.

<sup>d</sup> Monthly probability of progression from HCC<sub>S</sub> to HCC<sub>M</sub> = 0.089; monthly probability of progression from HCC<sub>M</sub> to HCC<sub>L</sub> = 0.056.

<sup>e</sup> AFP distributions derived from pooled individual patient data.<sup>10,287,293,326–328</sup>

<sup>f</sup> Rates calibrated to be in line with the mix of tumour sizes reported in Trevisani *et al.* (2002).<sup>278</sup>

<sup>g</sup> All patients have the same probability of receiving a transplant, regardless of reason for listing.

<sup>h</sup> Equivalent to a monthly probability of receiving a transplant = 0.254.

<sup>i</sup> Equivalent to a monthly probability of receiving a transplant = 0.242.

<sup>j</sup> Equivalent to a monthly probability of receiving a transplant = 0.267.

<sup>k</sup> Average of HBV and HCV values in absence of a reliable ALD-specific estimate.

<sup>l</sup> Assuming 33% of patients receive TACE.

**TABLE 10** Parameters used in Markov model: values affecting costs

Parameter	Value		Range of values used in sensitivity analyses	
			Lower	Upper
<b>Unit costs</b>				
AFP test	£4	per test	£2	£8
CT scan	£110	per scan	£50	£130
Ultrasound scan	£50	per scan	£26	£100
MRI scan	£200	per scan	£180	£400
Outpatient appointment	£101	per appointment	£72	£133
PEI	£754	per procedure	£377	£1,508
RFA	£381	per procedure	£190	£762
TACE	£537	per procedure	£268	£1,074
<b>State costs</b>				
All compensated cirrhosis states	£1,171	per year	£718	£1,624
All decompensated cirrhosis states	£9,385	per year	£6,407	£12,363
All known HCC states	£1,230	extra <sup>a</sup> per year	£615	£2,460
OLT	£21,800	per operation	£16,700	£31,800
Post-OLT (year 1)	£9,872	per patient per year	£4,831	£14,921
Post-OLT (year 2 onwards)	£1,564	per patient per year	£821	£2,315
Resection	£5,400	per operation	£1,500	£6,000
Postresection	£3,532	per patient per year	£2,338	£4,763
Palliative care (HCC <sub>S</sub> and HCC <sub>M</sub> )	£1,619	extra <sup>b</sup> per year	£809	£3,237
Palliative care (HCC <sub>L</sub> )	£177	extra <sup>b</sup> per year	£88	£354
<b>Event costs</b>				
False-positive diagnosis	£512	per false-positive diagnosis	£374	£796
Symptomatic/incidental diagnosis	£164	per diagnosis	£78	£238

<sup>a</sup> In addition to costs of underlying cirrhosis.

<sup>b</sup> In addition to costs of underlying cirrhosis and costs of HCC.

TABLE 11 Parameters used in Markov model: utilities

Health state	Markov states applied to	Value	Source	Range of values used in sensitivity analyses	
				Lower	Upper
Compensated cirrhosis	All compensated cirrhosis states ( $\pm$ known or occult HCC <sub>S</sub> or HCC <sub>M</sub> , including patients on the OLT waiting list)	0.75	Chong <i>et al.</i> , 2003 <sup>312</sup>	0.66	0.83
Decompensated cirrhosis	All decompensated cirrhosis states ( $\pm$ known or occult HCC <sub>S</sub> or HCC <sub>M</sub> , including patients on the OLT waiting list)	0.66	Chong <i>et al.</i> , 2003 <sup>312</sup>	0.46	0.86
HCC	Terminal HCC <sub>L</sub>	0.64	Chong <i>et al.</i> , 2003 <sup>312</sup>	0.44	0.86
Month of OLT	OLT (month of)	0.50	AA	0.30	0.60
Post-OLT (year 1)	Post-OLT (year 1)	0.69	Ratcliffe <i>et al.</i> , 2002 <sup>318</sup>	0.64	0.74
Post-OLT (year 2+)	Post-OLT (year 2 onwards)	0.73	Ratcliffe <i>et al.</i> , 2002 <sup>318</sup>	0.67	0.78
Month of resection	Resection (month of)	0.50	AA	0.30	0.60
Postresection	Postresection (survivors)	0.73	<sup>a</sup>	0.62	0.84

<sup>a</sup> Weighted average of values adopted for compensated and decompensated cirrhosis, calculated to approximate average clinical course following resection, including probability of decompensation.

Performed consecutively, these two calculations are equivalent to:

$$1 - prob^{-(1/time)}$$

where *time* is the number of units of interest spanned in the probability. For example, annual probabilities were converted to monthly ones using the formula  $1 - prob^{(1/12)}$ .

## Discounting

In accordance with HM Treasury advice, costs and benefits are discounted at 3.5%. The impact of discounting on the results was explored using the following rates: 1.5%, 3%, 4.5% and 6%. Undiscounted results are also presented.

## Dealing with uncertainty

### One-way sensitivity analysis

Extensive one-way sensitivity analyses were undertaken to explore which of the input parameters, when varied in isolation, have the greatest impact on the results. For simplicity, a single core comparison was used: 6-monthly AFP and ultrasound versus no surveillance in a mixed cohort.

In some of the analyses of uncertainty the results are expressed in terms of net monetary benefit. Net monetary benefit is an alternative method of combining the outputs (marginal cost and marginal benefit) from the cost–utility model. It is calculated by first assigning a cost value to a benefit unit. The marginal benefit of the treatment arm of the model can then be rescaled in terms of cost using this valuation. If a QALY is valued at £30,000, for example, then a marginal benefit of 100 QALYs between arms is valued at £3,000,000. The net monetary benefit of the treatment can then be calculated by simply offsetting the marginal cost against the marginal benefits of treatment (i.e. the benefit difference between arms expressed in pounds minus the cost difference expressed in pounds). The advantage of using net monetary benefit as an output metric is that it is a more intuitive measure of output and behaves in a more linear way than the incremental cost-effectiveness ratio (ICER). It is hence much easier to interpret. The main downside of using net monetary benefit is that it relies on a specific level of valuation for each unit of benefit. The present analysis used the commonly applied valuation of £30,000 per QALY.

Inputs used in the one-way sensitivity analyses are shown in *Tables 8–11*.

**TABLE 12** Parameters used in scenario in which transplantation is the only possible curative treatment option

Parameter	Cohort	Value	Source	Range of values used in sensitivity analyses	
				Lower	Upper
Proportion with HCC <sub>S</sub> who are listed for OLT	All	95%	AA	90%	98%
Proportion with HCC <sub>S</sub> who are deemed surgically untreatable	All	5%	AA	10%	2%
Proportion with HCC <sub>M</sub> who are listed for OLT	All	90%	AA	80%	95%
Proportion with HCC <sub>M</sub> who are deemed surgically untreatable	All	10%	AA	20%	5%
Proportion with HCC <sub>L</sub> who are deemed surgically untreatable	All	100%	AA	–	–

## Scenario analyses

Several scenario analyses were also performed.

### Compliance

The effects of compliance on the cost-effectiveness analysis were explored in two ways: in a scenario analysis and in a detailed one-way sensitivity analysis. Two types of non-compliance were considered: (i) not all appointments are attended, everyone has an equal probability of attending or missing the appointment and (ii) a proportion of people discontinue participation in the programme altogether. In the scenario analysis two levels of non-compliance were considered: 50% of appointments are missed with 5% dropping out of the programme per year and 75% of appointments are missed with 10% of people dropping out of the programme per year.

### Tumour growth rate

For each aetiology of cirrhosis, nine separate analyses were performed, with both of the tumour growth rates that are specified in the model (HCC<sub>S</sub> to HCC<sub>M</sub> and HCC<sub>M</sub> to HCC<sub>L</sub>) varied simultaneously over nine equal strata, corresponding to tumour volume doubling times from 80 to 203 days (the 95% confidence interval reported in the selected parameter source for tumour growth rate;<sup>324</sup> see below). The results of these analyses were then pooled, with a weighted average cost, utility and cost-utility calculated according to three separate distributions: a normal distribution (approximating a similar number of slow-growing and fast-growing tumours) and two beta distributions (approximating a preponderance of slow-growing and fast-growing tumours, respectively).

### Transplant as the only surgical treatment option

An analysis was performed in which the only treatment option is transplant. The number of patients listed for transplant or who were deemed unsuitable for surgical treatment was based on simple proportions and varied according to tumour size (*Table 12*).

### More effective, more expensive ultrasound

An analysis was performed in which the cost and effectiveness of ultrasound were increased to reflect potential improvements in ultrasound technology. Further details are provided in the section 'More effective, more expensive ultrasound' (p. 85).

### Alternative AFP sensitivity data

An analysis was performed using alternative data on the diagnostic accuracy of AFP assay obtained from a report published by Farinati and co-workers.<sup>329</sup> This was not an a priori analysis as the data came to our attention in the latter stages of preparation of this report. The data originate from a consecutive series of more than 1000 Italian patients with HCC. More details are provided in the section 'Alternative AFP sensitivity data' (p. 88).

### Detailed one-way sensitivity analyses

Several detailed one-way sensitivity analyses were performed in which parameters (or related groups of parameters) of interest were varied while all other values, which may themselves be subject to uncertainty, were held at their base-case values. These analyses were performed over wide ranges of possible parameter

values for various reasons which are explained in more detail below.

**Compliance**

In this analysis, because there is little evidence to inform the nature of non-compliance with surveillance, the two parameters which define the probability that screening appointments will be met were varied over a range of correlated values. The likelihood of any individual test cycle being performed ranged from 25 to 100% and, simultaneously, the proportion of the cohort dropping out of the programme entirely was varied from 10% per annum to nil.

**Tumour growth rate**

In addition to the scenario analysis described above, a one-way analysis was performed in which the effect of varying the average rate at which all tumours in the base case of the model are assumed to grow was investigated.

**Sensitivity of ultrasound**

As it is possible that the research literature-derived values surrounding ultrasound test performance may not reflect current practice or technological developments, an analysis was performed in which the parameters defining the sensitivity of ultrasound for detecting tumours were simultaneously varied over a range of correlated values from 5 to 50%, 10 to 75% and 50 to 100% for small, medium and large HCCs, respectively.

**Cost of AFP test**

The low cost of the AFP test may be important in the finding that surveillance with AFP as the initial test is always cheaper and always more cost-effective than surveillance with ultrasound at the same frequency. Therefore, a threshold analysis was performed on the cost of AFP, which examines model outputs as this unit cost is increased. As this analysis examines the impact of a cost input, the

results are expressed in terms of cost-effectiveness, expressed as net monetary benefit at a willingness-to-pay (WTP) threshold of £30,000 per QALY, as a function of the cost of the AFP test.

**Probabilistic sensitivity analysis**

Probabilistic sensitivity analysis (PSA) was also undertaken. A Monte Carlo simulation was developed to explore the impact of underlying parameter uncertainty on cost-effectiveness. In the stochastic approach, the Markov model is run for 10,000 trials with key input values randomly drawn from probabilistic density functions in each model run. In these simulated trials, values were sampled for transition probabilities, utilities and costs, using the distributions as shown in Tables 13–16.

Wherever possible, we relied on the sample sizes in the research on which the base-case parameter estimate is based (denoted *n*). However, in some instances these sample sizes were so small that they created nonsensical results, so for these parameters a higher notional sample size (denoted *N*) was arbitrarily used. The uncertainty in all binary probability parameters was assumed to have a beta distribution, most cost parameters a log-normal distribution and the parameter age at diagnosis a normal distribution. Dirichlet distributions were used for probability parameters where there were more than two chance outcomes.

**Value of information analyses**

Expected value of perfect information (EVPI) analysis uses PSA outputs to assess the likely costs of making a poor decision based on the available data, and hence provides a measure of the maximum monetary value of having perfect information. Hence, the global EVPI provides a notional upper estimate of the total cost of further research that might better inform the parameters

**TABLE 13** Parameters varied in probabilistic model simulations: cohort characteristics

Parameter	Distribution	Cohort	Parameters of the distribution	Expected value
Mean age of starting cohort (age of diagnosis of cirrhosis)	Normal	ALD	Mean = 53; SD = 4/√(500)	53
		HBV	Mean = 44; SD = 4/√(500)	44
		HCV	Mean = 54; SD = 4/√(500)	54
Gender mix of cohort (% male)	Beta	ALD	<i>n</i> = 301; <i>r</i> = 211	0.70100
		HBV	<i>n</i> = 349; <i>r</i> = 302	0.86533
		HCV	<i>n</i> = 384; <i>r</i> = 223	0.58073
Upper age limit for surveillance programmes	Log-normal	All	<i>u</i> (mean of logs) = ln(70); sigma (SD of logs) = ln(80/60)/√(2000)	70.00145

**TABLE 14** Parameters varied in probabilistic model simulations: values affecting transition probabilities

Parameter	Distribution	Cohort	Parameters of the distribution	Expected value
Annual incidence of cirrhosis decompensation	Beta	ALD	$n = 161; r = 5$	0.03106
		HBV	$n = 161; r = 5$	0.03106
		HCV	$n = 136; r = 7$	0.05147
Annual incidence of HCC	Beta	ALD	$n = 584; r = 10$	0.01712
	Beta	HBV	$n = 401; r = 9$	0.02244
	Beta	HCV	$n = 1284; r = 47$	0.03660
Tumour growth rate (small to medium)	Beta	All	$n = 16; r = 8$	0.5
Tumour growth rate (medium to large)	Beta	All	$n = 16; r = 6$	0.375
AFP distribution in HCC <sub>S</sub>	Dirichlet	All	Alphas list = List(352;568;80)	
AFP distribution in HCC <sub>M</sub>	Dirichlet	All	Alphas list = List(378;500;122)	
AFP distribution in HCC <sub>L</sub>	Dirichlet	All	Alphas list = List(222;444;334)	
AFP distribution in patients with no HCC	Dirichlet	All	Alphas list = List(906;88;6)	
Probability of detection of HCC <sub>S</sub> by ultrasound	Beta	All	$N = 500; r = 54$	0.108
Probability of detection of HCC <sub>M</sub> by ultrasound	Beta	All	$N = 500; r = 143$	0.286
Probability of detection of HCC <sub>L</sub> by ultrasound	Beta	All	$N = 500; r = 375$	0.75
False-positive rate for ultrasound	Beta	All	$N = 500; r = 17$	0.034
False-positive rate for CT	Beta	All	$N = 600; r = 539$	0.89833
Annual symptomatic/incidental presentation rate for HCC <sub>S</sub>	Beta	All	$N = 10000; r = 160$	0.016
Annual symptomatic/incidental presentation rate for HCC <sub>M</sub>	Beta	All	$N = 1000; r = 121$	0.121
Annual symptomatic/incidental presentation rate for HCC <sub>L</sub>	Beta	All	$N = 1000; r = 500$	0.5
Proportion with decompensated cirrhosis who are listed for OLT	Beta	All	$N = 1000; r = 900$	0.9
Proportion with HCC <sub>S</sub> who are listed for OLT	Beta	All	$N = 1000; r = 950$	0.95
Proportion with HCC <sub>S</sub> who receive resection	Beta	All	$N = 500; r = 100$	0.2
Proportion with HCC <sub>M</sub> who are listed for OLT	Beta	All	$N = 1000; r = 900$	0.9
Proportion with HCC <sub>M</sub> who receive resection	Beta	All	$N = 500; r = 25$	0.05
Monthly probability of receiving an OLT once on waiting list	Beta	All	$n = 2271; r = 577$	0.25407
Annual mortality rate due to decompensated cirrhosis	Beta	ALD	$n = 98; r = 17$	0.17347
		HBV	$n = 33; r = 7$	0.21212
		HCV	$n = 65; r = 8$	0.12308
Mortality rate for patients following OLT	Log-normal	All	$u$ (mean of logs) = 0; sigma (SD of logs) = $0.3/\sqrt{2000}$	1.00002
Mortality rate for patients following resection	Log-normal	All	$u$ (mean of logs) = 0; sigma (SD of logs) = $0.3/\sqrt{2000}$	1.00002
Annual mortality rate associated with occult HCC <sub>L</sub>	Beta	All	$n = 194; r = 141$	0.72680
Annual mortality rate associated with known HCC <sub>L</sub>	Beta	All	$N = 100; r = 66$	0.66

**TABLE 15** Parameters varied in probabilistic model simulations: values affecting costs

Parameter	Distribution	Cohort	Parameters of the distribution	Expected value
<b>Unit costs</b>				
AFP test	Log-normal	All	$u$ (mean of logs) = $\ln(4)$ ; sigma (SD of logs) = $(\ln(8/2)/4)/\sqrt{(8)}$	4.03
CT scan	Log-normal	All	$u$ (mean of logs) = $\ln(110)$ ; sigma (SD of logs) = $(\ln(130/50)/4)/\sqrt{(130)}$	110.02
Ultrasound scan	Log-normal	All	$u$ (mean of logs) = $\ln(50)$ ; sigma (SD of logs) = $(\ln(100/26)/4)/\sqrt{(135)}$	50.02
<b>State costs</b>				
All compensated cirrhosis states	Log-normal	All	$u$ (mean of logs) = $\ln(1171)$ ; sigma (SD of logs) = $\ln(2479)/\sqrt{(1150)}$	1202.52
All decompensated cirrhosis states	Log-normal	All	$u$ (mean of logs) = $\ln(9385)$ ; sigma (SD of logs) = $\ln(9610)/\sqrt{(1500)}$	9651.81
All known HCC states	Log-normal	All	$u$ (mean of logs) = $\ln(1230)$ ; sigma (SD of logs) = $(\ln(2460/615)/4)/\sqrt{(20)}$	1233.70
OLT	Log-normal	All	$u$ (mean of logs) = $\ln(21800)$ ; sigma (SD of logs) = $(\ln(31800/16700)/1.35)/14$	21812.66
Post-OLT	Log-normal	All	$u$ (mean of logs) = 0; sigma (SD of logs) = $0.25/\sqrt{(500)}$	1.00006
Resection	Log-normal	All	$u$ (mean of logs) = $\ln(5400)$ ; sigma (SD of logs) = $(\ln(6000/1500)/1.35)/\sqrt{(131)}$	5421.78
Postresection	Log-normal	All	$u$ (mean of logs) = $\ln(3532)$ ; sigma (SD of logs) = $(\ln(4763/2338)/4)/\sqrt{(115)}$	3532.49
Palliative care (HCC <sub>S</sub> and HCC <sub>M</sub> )	Log-normal	All	$u$ (mean of logs) = $\ln(1618.65)$ ; sigma (SD of logs) = $(\ln(3237.3/809.16)/4)/\sqrt{(50)}$	1620.60
Palliative care (HCC <sub>L</sub> )	Log-normal	All	$u$ (mean of logs) = $\ln(177.21)$ ; sigma (SD of logs) = $(\ln(354.22/88.44)/4)/50$	177.21
<b>Event costs</b>				
False-positive diagnosis	Log-normal	All	$u$ (mean of logs) = $\ln(512)$ ; sigma (SD of logs) = $(\ln(796/374))/\sqrt{(124)}$	513.18

**TABLE 16** Parameters varied in probabilistic model simulations: utilities

Parameter	Distribution	Cohort	Parameters	Expected value
Compensated cirrhosis	Beta	All	$N = 500$ ; $r = 375$	0.75
Decompensated cirrhosis	Beta	All	$N = 100$ ; $r = 9$	0.09
HCC	Beta	All	$N = 100$ ; $r = 11$	0.11
Post-OLT	Log-normal	All	$u$ (mean of logs) = 0; sigma (SD of logs) = 0.16	1.01288
Postresection	Log-normal	All	$u$ (mean of logs) = 0; sigma (SD of logs) = $0.3/\sqrt{(2000)}$	1.00002

in the analysis.<sup>330</sup> Owing to limitations of computational capacity and time, no estimates were calculated of the value of perfect information

(i.e. minimising the uncertainty) in relation to particular parameters or groups of parameters (that is, partial EVPI analysis).



## Chapter 4

# Cost-effectiveness model: parameters

### Overriding principles

For all estimates, attempts were made to find a source that had a large sample size, consisted of UK patients with a diagnosis of cirrhosis (with details of cirrhosis aetiology) and was a recently published study. For parameters in which there were no UK-based studies available, sources from countries with a similar disease profile were sought (see the section 'Epidemiology and natural history of hepatic cirrhosis', p. 1).

Initially, three additional literature searches for model parameter estimates were performed in electronic databases in the following areas (full details are provided in Appendix 2):

- natural history and progression of cirrhosis and HCC
- effectiveness and harms of treatments for HCC
- quality of life associated with cirrhosis, HCC and surveillance.

The search strategies were developed, tested and refined by an information scientist (AP). All searches were limited to English-language papers in humans. The search for articles relating to the natural history and progression of cirrhosis and HCC was limited to the years 2002–2005 to reduce the number of results. Searches were not limited by methodological features. Reference lists from retrieved articles were studied and additional papers were identified following contacts with experts.

During the implementation of the model, particular efforts were taken to obtain relevant literature in areas where there was a paucity of data in these initial searches. Additional searches, which were not limited by publication date, were therefore performed in the following areas:

- quality of life associated with cirrhosis, HCC and surveillance
- cost-effectiveness of surveillance
- survival following transplant, resection and other palliative treatments
- test performance of AFP, ultrasound and CT
- tumour growth rate.

In some cases, data were obtained from unpublished sources; further details are provided below.

### Selection of parameters: baseline characteristics

#### Age at diagnosis of cirrhosis

Nineteen studies were identified that fulfilled the initial criteria and described the age of patients at diagnosis of cirrhosis.<sup>5,6,8,22,36,64,68,98,331–333</sup> Thirteen studies were excluded.<sup>5,6,8,10,68,284,287,289,293,298,333</sup>

Details of the studies are shown in *Table 17*.

#### Alcoholic cirrhosis

The three short-listed studies provided very similar estimates. For the base case, the value from Roberts and co-workers' analysis<sup>36</sup> was chosen, as it was a recent study, based on a large UK sample. The one-way sensitivity analysis explored the impact of varying this mean value by an exaggerated amount ( $\pm$  an arbitrary 10 years), in order to observe the extent to which the model was sensitive to this parameter, even though it was relatively certain that the true population mean lies close to the point estimate used in the base case. (In the PSA the standard deviation was used to specify the uncertainty of this parameter.)

#### HBV-related cirrhosis

None of the studies provides data from the UK. The three short-listed estimates are similar; however, since the study by Fattovich and colleagues<sup>98</sup> represents a larger overall sample size, a mean age of 44 years was used for the age of diagnosis of cirrhosis in patients with HBV. Again, this value was varied by  $\pm$  10 years in the one-way sensitivity analysis.

#### HCV-related cirrhosis

None of the studies provides data exclusively from UK patients; however, the study by Fattovich and co-workers<sup>64</sup> included one UK centre (providing 14 patients to the sample; G Fattovich: personal communication, October 2005). As this study represents a slightly larger sample size, from a European population, a mean age of 54 years was used for the age of diagnosis of cirrhosis in patients with HCV. This value was varied by  $\pm$  10 years in the one-way sensitivity analysis.

**TABLE 17** Selection of parameter estimates: age at diagnosis of cirrhosis

19 studies reviewed:						
<b>Studies excluded (13):</b>						
<ul style="list-style-type: none"> <li>• Reported age at entry into surveillance programme, not age at diagnosis of cirrhosis (2)<sup>22,296</sup></li> <li>• Reported combined results for mixed cirrhosis aetiologies (9)<sup>6,8,10,68,284,287,289,293,298</sup></li> <li>• Reported median age (1)<sup>333</sup></li> <li>• Broad age range data only reported (1)<sup>5</sup></li> </ul>						
<b>Data extracted from six studies:</b>						
	Study	Country	Years	Aet.	N	Mean age (years)
<b>Studies rejected (3)</b>	Saunders <i>et al.</i> , 1981 <sup>331</sup>	UK	1959–1976	ALD	242	53 <sup>a</sup>
	del Olmo <i>et al.</i> , 1998 <sup>332</sup>	Spain	NS	ALD	327	51.2
	Chiaromonte <i>et al.</i> , 1999 <sup>285</sup>	Italy	1981–1993	HBV	66	44.8
	del Olmo <i>et al.</i> , 1998 <sup>332</sup>	Spain	NS	HBV	111	44.5
	Chiaromonte <i>et al.</i> , 1999 <sup>285</sup>	Italy	1981–1993	HCV	166	55.5
	del Olmo <i>et al.</i> , 1998 <sup>332</sup>	Spain	NS	HCV <sup>b</sup>	597	55.8
<b>Studies selected</b>	Roberts <i>et al.</i> , 2005 <sup>36</sup>	UK	1966–1999	ALD	2802	53.3 (SD 12.4)
	Fattovich <i>et al.</i> , 1995 <sup>98</sup>	Europe <sup>c</sup>	1973–1991	HBV	349	44 (range 17–74)
	Fattovich <i>et al.</i> , 1997 <sup>64</sup>	Europe <sup>d</sup>	1982–1992	HCV	384	54 (SD 4.93)
Aet., aetiology; NS, not stated. <sup>a</sup> Mean age for men (55.2 for women). <sup>b</sup> Including non-A/non-B hepatitis (185 patients identified before 1990). <sup>c</sup> Nine centres in Italy, Denmark, France, Greece, The Netherlands, Portugal and Spain. <sup>d</sup> Seven centres in Italy, Belgium, France, The Netherlands and the UK.						

### Gender mix at time of diagnosis of cirrhosis

The studies considered for this parameter were predominantly the same as those reviewed for baseline age estimates.<sup>5,6,8,22,36,64,68,98,284,286,296,331–333</sup> See *Table 18* for details.

#### Alcoholic cirrhosis

The UK studies considered suggest that between three- and four-fifths of patients with alcohol-related cirrhosis are men. Mortality statistics from the ONS registry suggest that the proportion is currently around 70% (i.e. in the middle of this range). As there is no reason to suspect that gender imparts a differential risk of mortality in alcohol-related cirrhosis, this figure was used as the base-case point estimate, and the proportion was varied between 50% (an arbitrary value to explore evidence that ALD is becoming more widespread among females<sup>334</sup>) and 90.2% (as per del Olmo and colleagues' findings<sup>332</sup>) in sensitivity analyses.

#### HBV-related cirrhosis

We concluded that the one UK study we had identified was based on too small a sample to be

reliable so, for the reasons discussed above, the same study used to inform the age parameter was adopted<sup>98</sup>. In the base case, the proportion of males within the simulated population of patients with HBV is therefore 86.5%. The reported 95% confidence intervals were used to define the range used in sensitivity analyses (82.6 to 89.7%).

#### HCV-related cirrhosis

As for HCV, the small UK study was rejected and the same study used to inform the age parameter<sup>64</sup> was relied on. In the base case, the proportion of males within the simulated population of patients with HCV is therefore 58.1%. The reported 95% confidence intervals were used to define the range used in sensitivity analyses (53.1 to 62.9%).

#### Composition of mixed cohort

The composition of the mixed cohort is the mean of three estimates obtained from the expert advisory group: 57.6% of the cohort has cirrhosis as a result of ALD, 35.1% have HCV-related cirrhosis and 7.3% have HBV-related cirrhosis.

**TABLE 18** Selection of parameter estimates: gender mix at diagnosis of cirrhosis

16 studies reviewed:						
<b>Studies excluded (6):</b>						
<ul style="list-style-type: none"> <li>• One study<sup>22</sup> appeared to repeat results presented in a larger cohort included below<sup>296</sup></li> <li>• Five studies reported combined results for mixed cirrhosis aetiologies<sup>6,8,68,284,286</sup></li> </ul>						
<b>Data extracted from ten studies:</b>						
	Study	Country	Years	Aet.	N	Gender mix
<b>Studies rejected (7)</b>	Saunders <i>et al.</i> , 1981 <sup>331</sup>	UK	1959–1976	ALD	242	66–80% male <sup>d</sup>
	Roberts <i>et al.</i> , 2005 <sup>36</sup>	UK	1966–1999	ALD	2802	61.3% male
	Douds <i>et al.</i> , 2005 <sup>5</sup>	UK	1987–2000	ALD	232	76.3% male
	Henrion <i>et al.</i> , 2003 <sup>296</sup>	Belgium	1995–1998	ALD	186	71.0% male
	del Olmo <i>et al.</i> , 1998 <sup>332</sup>	Spain	NS	ALD	327	90.2% male
	Douds <i>et al.</i> , 2005 <sup>5</sup>	UK	1987–2000	HBV	17	76.5% male
	Chiaramonte <i>et al.</i> , 1999 <sup>285</sup>	Italy	1981–1993	HBV	66	75.8% male
	del Olmo <i>et al.</i> , 1998 <sup>332</sup>	Spain	NS	HBV	111	80.2% male
	Douds <i>et al.</i> , 2003 <sup>5</sup>	UK	1987–2000	HCV	29	69.0% male
	Chiaramonte <i>et al.</i> , 1999 <sup>285</sup>	Italy	1981–1993	HCV	166	52.4% male
	Henrion <i>et al.</i> , 2003 <sup>296</sup>	Belgium	1995–1998	HCV	65	56.9% male
	Degos <i>et al.</i> , 2000 <sup>333</sup>	France	1987–1996	HCV	416	57.7% male
	del Olmo <i>et al.</i> , 1998 <sup>332</sup>	Spain	NS	HCV <sup>b</sup>	597	58.1% male
<b>Studies selected</b>	ONS mortality statistics <sup>c</sup>	England and Wales	1999–2003	ALD	827	70.1% male
	Fattovich <i>et al.</i> , 1995 <sup>98</sup>	Europe <sup>d</sup>	1973–1991	HBV	349	86.5% male
	Fattovich <i>et al.</i> , 1997 <sup>64</sup>	Europe <sup>e</sup>	1982–1992	HCV	384	58.1% male

<sup>a</sup> Ratio fell from 4:1 in 1959–1965 to 2:1 in 1971–1976.  
<sup>b</sup> Including non-A/non-B hepatitis (185 patients identified before 1990).  
<sup>c</sup> Office for National Statistics: *Mortality Statistics: Cause (Series DH2)*. 1999–2003. Available from: [www.statistics.gov.uk/Statbase/Product.asp?vlink=618](http://www.statistics.gov.uk/Statbase/Product.asp?vlink=618)  
<sup>d</sup> Nine centres in Italy, Denmark, France, Greece, The Netherlands, Portugal and Spain.  
<sup>e</sup> Seven centres in Italy, Belgium, France, The Netherlands and the UK.

## Selection of parameters: transitions

### Rate of incidence of HCC in patients with cirrhosis

Nine studies were identified that fulfilled the initial selection criteria.<sup>6,8,64,65,67,323,332,333,335</sup>

Details of the studies are shown in *Table 19*. None of the studies reported the incidence of HCC in patients with cirrhosis in the UK.

### Alcoholic cirrhosis

A review by Fattovich and colleagues<sup>323</sup> included two estimates of the incidence of HCC among patients with alcoholic cirrhosis. One estimate was derived from a series of three population-based studies and, although this included a large number of patients ( $n = 15,020$ ), diagnoses of HBV and HCV were not investigated. The second estimate also summarised the data from three studies, but involved 584 patients visiting liver clinics and excluded patients with HBV and HCV. The second estimate was therefore considered most appropriate for use in the model.

### HBV-related cirrhosis

Three papers included data on the incidence of HCC among patients with HBV.<sup>67,98,323</sup> Two were studies conducted in several European countries and the third a combined estimate from six studies performed in Italy ( $n = 5$ ) and Greece ( $n = 1$ ) which excluded patients treated with interferon. Estimates from all three sources were similar; the estimate used in the model was taken from the review as it involves the largest sample size and provides additional information of the variability surrounding the estimate.

### HCV-related cirrhosis

Five studies included data on patients with HCV. The study by Fattovich and colleagues<sup>64</sup> was excluded as the criteria for inclusion of patients in the study have been criticised for being too narrow; all patients with a history of alcohol abuse greater than 80 g per day for more than 5 years were excluded. Estimates from the four remaining studies are similar. An incidence rate of 3.7 per 100 person-years was chosen to populate the model because it was derived from the largest

**TABLE 19** Selection of parameter estimates: rate of incidence of HCC

Nine studies reviewed:								
<b>Studies excluded (3):</b> • Three studies <sup>6,8,332</sup> reported combined results for mixed cirrhosis aetiologies								
<b>Data extracted from six studies:</b>								
	Study	Country	Years	Aet.	N	HCC incidence rate	Equiv. annual rate	Equiv. monthly rate
<b>Studies rejected (5)</b>	Fattovich <i>et al.</i> , 2004 <sup>323</sup>	Europe <sup>a</sup>	1965–	ALD <sup>b</sup>	15,020	0.2/100 person-years	0.2%	0.02%
	Fattovich <i>et al.</i> , 1995 <sup>98</sup>	Europe <sup>c</sup>	1973–1991	HBV	349	3% at 3 years 6% at 5 years 15% at 10 years	1.0% 1.2% 1.6%	0.08% 0.10% 0.14%
	Fattovich <i>et al.</i> , 2002 <sup>67</sup>	Europe <sup>c</sup>	1982–1992	HBV	161	2.2/100 person-years c5% at 3 years <sup>d</sup> 10% at 5 years c18% at 10 years <sup>d</sup>	2.2% 1.7% 2.1% 2.0%	0.19% 0.14% 0.18% 0.17%
	Fattovich <i>et al.</i> , 1997 <sup>64</sup>	Europe <sup>e</sup>	1982–1992	HCV	384	4% at 3 years 7% at 5 years 14% at 10 years	1.4% 1.4% 1.5%	0.11% 0.12% 0.13%
	Degos <i>et al.</i> , 2000 <sup>333</sup>	France	1987–1996	HCV	416	c10% at 3 years <sup>d</sup> 13.4% at 5 years c34% at 9 years <sup>d</sup>	3.5% 3.5% 4.5%	0.29% 0.30% 0.38%
	Serfaty <i>et al.</i> , 1998 <sup>65</sup>	France	1989–1994	HCV	103	3.3% per annum 11.5% at 4 years	3.3% 3.0%	0.28% 0.25%
	Fattovich <i>et al.</i> , 2002 <sup>67</sup>	Europe <sup>c</sup>	1982–1992	HCV	136	2.5/100 person-years c5% at 3 years <sup>d</sup> 9% at 5 years c27% at 10 years <sup>d</sup>	2.5% 1.7% 1.9% 2.0%	0.21% 0.14% 0.16% 0.17%
<b>Studies selected</b>	Fattovich <i>et al.</i> , 2004 <sup>323</sup>	Europe <sup>f</sup>	1973–1999	ALD <sup>g</sup>	584	1.7/100 person-years	1.7%	0.14%
		Europe <sup>h</sup>	1982–1997	HBV	401	2.2/100 person-years	2.2%	0.19%
		Europe <sup>i</sup>	1982–1999	HCV	1,284	3.7/100 person-years	3.7%	0.31%

Equiv., equivalent.  
<sup>a</sup> Synthesis of data from three papers<sup>336–338</sup> from Sweden (2) and Denmark (1).  
<sup>b</sup> Population-based series.  
<sup>c</sup> Nine centres in Italy, Denmark, France, Greece, The Netherlands, Portugal and Spain.  
<sup>d</sup> Estimated from published Kaplan–Meier graph; precise figures not specified.  
<sup>e</sup> Seven centres in Italy, Belgium, France, The Netherlands and the UK.  
<sup>f</sup> Using their synthesis of data from three papers<sup>8,296,339</sup> from Spain (2) and Belgium (1).  
<sup>g</sup> Liver clinic series.  
<sup>h</sup> Using their synthesis of data from six papers,<sup>67,285,340–343</sup> collecting data from 13 centres in Italy (5), Belgium, Denmark, France, Greece, The Netherlands, Portugal, Spain and the UK (one each).  
<sup>i</sup> Using their synthesis of data from 13 papers,<sup>8,65,67,102,285,333,340,341,344–348</sup> collecting data from 21 centres in Italy (7), France (4), Spain (2), Belgium, Denmark, Germany, Greece, Portugal, The Netherlands, the UK and the USA (one each).

sample size (a combined estimate from 13 studies involving 1284 individuals) and patients treated with interferon were excluded.

### Tumour growth rate

There are very few studies which evaluate the growth rate of HCC tumours. Extensive searching revealed a total of nine papers<sup>324,327,328,349–354</sup> (Table 20). We were unable to locate studies based on UK populations or studies in which the tumour growth rates in

patients with different cirrhosis aetiologies were reported.

It was felt that this aspect of the natural history of HCCs might be substantially affected by the underlying characteristics of the population. Accordingly, the six short-listed papers that originated in Asian countries were excluded. For the same reason, of the two remaining options, we were predisposed to prefer the US study over the Italian paper, although it was noted that these two

**TABLE 20** Selection of parameter estimates: tumour growth rate

Nine studies reviewed:						
<b>Studies excluded (1):</b> • Modelling study containing no primary data <sup>354</sup>						
<b>Data extracted from eight studies:</b>						
	Study	Country	Years	N	Tumour volume doubling time	
					Mean ± SD	Median (range)
<b>Studies rejected (7)</b>	Yoshino 1983 <sup>351</sup>	Japan	<sup>a</sup>	39	204.2 ± 135.00	171.6 (27–606)
	Sheu <i>et al.</i> , 1985 <sup>327</sup>	Taiwan	1981–1983	16	132.0 ± 94.00	95.0 (41–315)
	Ebara <i>et al.</i> , 1986 <sup>328</sup>	Japan	1979–1983	21	197.7 ± 173.38	(30–593)
	Barbara <i>et al.</i> , 1992 <sup>350</sup>	Italy	1984–1990	31	136.0 ± 94.21	117.0 (29–398)
	Saito <i>et al.</i> , 1998 <sup>353</sup>	Japan	1988–1993	21	207.5 ± 162.60	142.7 (76–720)
	Nakajima <i>et al.</i> , 2002 <sup>352</sup>	Japan	NS	34	90.8 ± 67.08	74.5 (17–274)
	Kubota <i>et al.</i> , 2003 <sup>349</sup>	Japan	1995–2002	22	114.9 ± 102.70	83.2 (33–496)
<b>Study selected</b>	Taouli <i>et al.</i> , 2005 <sup>324</sup>	USA	1997–2002	16 <sup>b</sup>	127.0 <sup>c</sup>	(18–541)
<sup>a</sup> “During the past three years” (study received January 1983).						
<sup>b</sup> 16 tumours in 11 patients.						
<sup>c</sup> The generalised estimation equation approach was used “to account for the correlation of lesions from the same patients”. Generalised estimation equation means were calculated first on their log-transformed values and then transformed back into the original scales.						

studies reported very similar mean tumour volume doubling times.

Taouli and colleagues' paper<sup>324</sup> reports a retrospective cohort and modelling study, describing the growth rate of 16 untreated tumours in 11 patients. Mean baseline and follow-up tumour volumes were 10.5 cm<sup>3</sup> (range 0.7–243.6 cm<sup>3</sup>) and 22.0 cm<sup>3</sup> (range 2.5–870.8 cm<sup>3</sup>), respectively. Mean tumour volume doubling time was 127 days (95% CI 80 to 203; range 17.5–541.4 days). Therefore, a mean tumour doubling time of 127 days was used to define tumour growth rate in patients with all three aetiologies of cirrhosis. In the absence of evidence to the contrary, the assumption was made that growth rates are constant, and a parameter estimate was applied to transitions from small to medium tumours and from medium to large tumours. For the range of values used in sensitivity analyses, the upper and lower bounds of the 95% confidence intervals reported in the chosen study were adopted. This range encompasses all the sample means reported in papers from which data were extracted.

### Rate of incidence of decompensation

We were unable to identify any cohort studies from the UK. When broadening the search to include data from other countries, a total of seven papers was identified. Three studies were excluded on preliminary review, in two cases because they were

considered out of date. The remaining four studies were considered in detail. Between them, the papers reported the incidence of decompensation in two cohorts of patients with HBV-related cirrhosis and three cohorts of patients with HCV-related cirrhosis. No studies were found reporting rates of decompensation in patients with alcohol-related cirrhosis. The data considered are collected in *Table 21*.

As far as posthepatic cirrhosis is concerned, it was felt that these studies represented a reliable and relatively homogeneous evidence base. Because the most recently published paper by Fattovich and colleagues<sup>67</sup> represents a large European study with a long follow-up period (median 79 months) and includes separate estimates for patients with HBV and HCV, this study was chosen to provide the base-case parameters, and the other estimates identified were used to inform the ranges used in sensitivity analyses.

We were unable to find any estimates of the incidence of decompensation in patients with alcoholic compensated cirrhosis. It was therefore assumed that the incidence would be similar to that occurring in patients with HBV, for two main reasons: first, ALD and HBV cohorts are comparable in terms of gender mix (which may be a covariate of decompensation probability) and, secondly, it was assumed that abstinent former

**TABLE 21** Selection of parameter estimates: rate of incidence of decompensation

Seven studies reviewed:								
<b>Studies excluded (3):</b>								
<ul style="list-style-type: none"> <li>• Two studies were based on cohorts recruited in the 1970s<sup>51,52</sup></li> <li>• One study concentrated on outcomes that were too wide ranging to correspond to the definition of decompensation<sup>355</sup></li> </ul>								
<b>Data extracted from four studies:</b>								
	Study	Country	Years	Aet.	N	Decompensation rate	Equiv. annual rate	Equiv. monthly rate
<b>Studies rejected (3)</b>	Fattovich <i>et al.</i> , 1995 <sup>98</sup>	Europe <sup>a</sup>	1973–1991	HBV	317 <sup>b</sup>	4% at 1 year <sup>c</sup> 17% at 3 years 23% at 5 years	4.0% 6.0% 5.1%	0.34% 0.52% 0.44%
	Fattovich <i>et al.</i> , 1997 <sup>64</sup>	Europe <sup>a</sup>	1982–1992	HCV	355 <sup>b</sup>	4% at 1 year <sup>c</sup> 12% at 3 years 18% at 5 years	4.0% 4.2% 3.9%	0.34% 0.35% 0.33%
	Hu <i>et al.</i> , 1999 <sup>66</sup>	USA	1990–1995	HCV	112	5% at 1 year <sup>c</sup> 17.3% at 3 years 22.2% at 5 years	5.0% 6.1% 4.9%	0.43% 0.53% 0.42%
<b>Study selected</b>	Fattovich <i>et al.</i> , 2002 <sup>67</sup>	Europe <sup>a</sup>	1982–1992	HBV	161	3.3/100 person-years 6% at 1 year <sup>c</sup> 14% at 3 years <sup>c</sup> 16% at 5 years	3.3% 6.0% 4.9%	0.27% 0.51% 0.42%
				HCV	136	5.3/100 person-years 7% at 1 year <sup>c</sup> 21% at 3 years <sup>c</sup> 28% at 5 years	5.3% 7.0% 7.6%	0.44% 0.60% 0.65%
<sup>a</sup> Nine centres in Italy, Denmark, France, Greece, The Netherlands, Portugal and Spain. <sup>b</sup> Excluding patients who developed HCC. <sup>c</sup> Estimated from published Kaplan–Meier graph; precise figures not specified.								

drinkers, having effectively eliminated the source of ongoing liver damage, were likely to experience decompensation rates at the lower end of the range observed. Accordingly, the HBV cohort’s annual incidence rate of 3.3% was duplicated for the ALD group, and the impact of this assumption was explored by varying the rate across the full range seen in all aetiologies in sensitivity analyses. Accordingly, the study used a rate of incidence of decompensation of 3.3% per year for patients with HBV and alcoholic cirrhosis and 5.3% per year for patients with HCV.

Anecdotal evidence suggests that the rate of decompensation in patients with HCC may be higher than in patients without HCC, but we were unable to find any significant evidence from the literature to substantiate this. Therefore, the rate of decompensation was varied from 1.8% to 7.0% for patients with alcoholic cirrhosis, from 1.8% to 6% for patients with HBV and from 3.9% to 7.0% in patients with HCV.

### Rate of incidental/symptomatic diagnosis of HCC

In the modelling of surveillance programmes, a particular problem is the estimation of incidental/symptomatic presentation (i.e. the likelihood that individuals with tumours will come to attention outside surveillance interventions; even those under surveillance may become symptomatic before their HCCs are screen detected). Of course, it is impossible to rely on published literature to characterise the natural history of unknown tumours, so it is necessary to rely on surrogate measures.

The model was calibrated to the data reported in Trevisani and colleagues’ retrospective cohort study,<sup>278</sup> because this paper provided a variety of measures against which model outputs could be checked. In particular, we sought to approximate the following findings:

- The proportion of unsurveilled patients who present with small and medium HCCs was

calculated with reference to Trevisani and co-workers' reporting of tumours that came to attention while 'non-advanced' (i.e. meeting the Milan criteria for transplantation; this was taken to equate to the present definition of 'small' and 'medium' tumours):  $139/449 = 31.0\%$ .

- The model's predictions were checked against the reported proportion of patients who presented symptomatically despite being under surveillance:  $29/215 = 13.5\%$  among those under 6-monthly follow-up and  $25/155 = 16.1\%$  for those being assessed annually.

A simplified version of the first phase of the natural history model was constructed in Microsoft Excel and used to predict the values that would enable these results to be replicated most accurately. This provided estimated annual symptomatic/incidental presentation rates of 1.6% for small HCCs (equivalent monthly rate 0.14%) and 12.1% for medium HCCs (equivalent monthly rate 1.1%).

It was assumed that large tumours would become symptomatic at a rate of 50% per year (5.6% per month).

### Compliance with the surveillance programme

There are very few published data presenting detailed information regarding compliance with

surveillance programmes in patients with cirrhosis (Table 22). Only one relevant UK study was found, but this is currently only available as an abstract.<sup>356</sup>

In the base case, 100% compliance with the surveillance programme is assumed. However, compliance is clearly an important factor in the success of a surveillance programme, and various types of non-compliance were explored in sensitivity analyses (see the sections 'Scenario analyses', p. 80, and 'Detailed one-way sensitivity analyses', p. 89).

### Test performance

The evidence base relating to diagnostic test performance was assessed with reference to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool developed by Whiting and co-workers.<sup>357</sup> In particular, we were keen to ensure that studies had assessed the test in question against an adequate reference ('gold') standard. In diagnosis of HCC, the optimal reference standard is pathological examination of the liver. Because patients who have been listed for transplantation due to liver failure may have undiagnosed HCCs, such patients comprise an ideal population in whom to assess the accuracy of diagnostic tests: the test is carried out while the patient is awaiting transplantation and, following the procedure, test

**TABLE 22** Selection of parameter estimates: patient compliance with surveillance programmes

Data extracted from 12 studies:									
Study	Country	Pop.	N	Freq.	Median follow-up (months) (range)	Irregular attendance		Complete dropout	
						n (%)	n (%)	Equiv. annual rate	Equiv. monthly rate
Henrion <i>et al.</i> , 2000 <sup>22</sup>	Belgium	ALD	86	6	34	11 (12.8%)		23.0%	2.155%
Henrion <i>et al.</i> , 2003 <sup>296</sup>	Belgium	ALD	172	6	60	26 (15.1%)	97 (56.4%)	15.3%	1.374%
Henrion <i>et al.</i> , 2000 <sup>22</sup>	Belgium	HCV	30	6	34	5 (16.7%)	1 (3.3%)	1.2%	0.100%
Henrion <i>et al.</i> , 2003 <sup>296</sup>	Belgium	HCV	64	6	60	4 (6.3%)	11 (17.2%)	3.7%	0.314%
Woodall <i>et al.</i> , 2002 <sup>356</sup>	UK	HCV	100	≤6	48		11 (11.0%)	2.9%	0.242%
Benvegnù <i>et al.</i> , 1994 <sup>283</sup>	Italy	Mixed	290	6	46.3 <sup>a</sup> (8–96)		38 (13.1%)	3.6%	0.303%
Bolondi <i>et al.</i> , 2001 <sup>68</sup>	Italy	Mixed	313	6	56 <sup>a</sup> (6–100)		24 (7.7%)	1.7%	0.142%
Borzio <i>et al.</i> , 1995 <sup>284</sup>	Italy	Mixed	307	6	43 <sup>a</sup> (12–95)		34 (11.1%)	3.0%	0.255%
Colombo <i>et al.</i> , 1991 <sup>286</sup>	Italy	Mixed	447	3–12	33		55 (12.3%)	4.7%	0.397%
Oka <i>et al.</i> , 1990 <sup>10</sup>	Japan	Mixed	140	2–3	36.2 (2–72)		26 (18.6%)	6.6%	0.566%
Pateron <i>et al.</i> , 1994 <sup>6</sup>	France	Mixed	118	6	36 (4–48)	21 (17.8%)	4 (3.4%)	1.1%	0.096%
Sangiovanni <i>et al.</i> , 2004 <sup>291</sup>	Italy	Mixed	417	6–12	148 (1–213)		165 (39.6%)	4.0%	0.340%
Solmi <i>et al.</i> , 1996 <sup>298</sup>	Italy	Mixed	406	6	56 <sup>a</sup> (18–72)		46 (11.3%)	5.4%	0.461%
Velazquez <i>et al.</i> , 2003 <sup>8</sup>	Spain	Mixed	463	3–6	38.6 <sup>a</sup> (1–96)		35 (7.6%)	2.4%	0.203%

Freq., frequency; pop., population.  
<sup>a</sup> Mean.

**TABLE 23** Selection of parameter estimates: ultrasound test performance

Nine studies reviewed:								
<b>Studies excluded (4):</b> • Insufficient detail regarding size of tumours detected/missed <sup>260,262,269,358</sup>								
<b>Data extracted from five studies:</b>								
	Study	Country	Years	N	HCC	Specificity	Size (diameter) (cm)	Sensitivity
<b>Studies rejected (4)</b>	Dodd <i>et al.</i> , 1992 <sup>259</sup>	USA	1990–1991	200	34 <sup>a</sup>	97.6%	<1 1–3 >3	29.4% 42.9% 68.0%
	Kim <i>et al.</i> , 2001 <sup>257</sup>	Korea	1996–1999	52	18	91.7%	<2 2–5	30.0% 37.5%
	Liu <i>et al.</i> , 2003 <sup>258</sup>	Korea	1996–2001	118	31	96%	<2 >2	13.8% 45.5%
	Rode <i>et al.</i> , 2001 <sup>261</sup>	France	1996–1997	43	6	94.6%	<1 1–2 >2	37.5% 50.0% 100.0%
<b>Study selected</b>	Bennett <i>et al.</i> , 2002 <sup>256</sup>	USA	1991–2000	200	27	96.5%	<2 2–5 >5	10.7% 28.6% 75.0%
<sup>a</sup> All malignancies, of which 28 (82%) were HCC.								

results can be compared to the explanted liver. Several studies have assessed the accuracy of various methods of HCC detection in this setting and, where possible, we sought to rely on these for the model parameters.

### Ultrasound examination

The search was limited to studies reporting the accuracy of ultrasound when measured against the reference standard of explant pathology in transplantation series. Nine such studies were identified, details of which are shown in *Table 23*. For the purposes of the model, it was crucial to capture the performance of ultrasound in detecting tumours of various sizes. Therefore, studies were excluded if they provided insufficient detail about the diameter of nodules found and missed.

Because abdominal ultrasonography is a rapidly advancing specialism, Dodd and co-workers' data<sup>259</sup> were considered unreliable, as they were collected 15 years ago (even though their results are comparable to those presented in the other studies considered). The two Korean papers were also discounted, as neither provides any evidence on the detectability of larger HCCs: no tumours in Kim and colleagues' series<sup>257</sup> exceed 5 cm in diameter and, although Liu and co-workers<sup>258</sup>

found tumours of up to 16 cm, available analyses only refer to tumours larger than 2 cm. Rode and colleagues' findings<sup>261</sup> are based on a small sample (43 liver explants, with HCC in six) and, owing to the exclusion of nodules smaller than 8 mm, the study almost certainly overestimates the capacity of ultrasound for detecting small HCCs.

Bennett and co-workers<sup>256</sup> present a more pessimistic view of the sensitivity of ultrasound, especially for the detection of small tumours, than the other analyses considered. However, we concluded that this study provides the most robust evidence currently available and, accordingly, drew the model parameters from this data.

It was presumed that the efficacy of ultrasound detection was likely to have a substantial effect on the outputs of the model, and the impact of these parameters was explored in extensive sensitivity analyses (see the section 'Detailed one-way sensitivity analyses', p. 89). As well as testing the model's reliance on these data, the effect of increasingly accurate first line imaging was simulated. Accordingly, scenarios were constructed and explored reflecting what may be anticipated from future technological progress in this area (see the section 'Scenario analyses', p. 80).



**TABLE 24** Selection of parameter estimates: AFP level in HCCs according to tumour size (sensitivity of test)

25 studies reviewed:								
<b>Studies excluded (13):</b>								
<ul style="list-style-type: none"> <li>• Ten papers provided insufficient data regarding tumour size<sup>40,251,262,292,294,359–363</sup></li> <li>• One study adopted thresholds that could not be mapped on to our project<sup>364</sup></li> <li>• One study reported a cohort of patients identified by AFP-only surveillance (so data exclude low-AFP cases)<sup>365</sup></li> <li>• One study reported results that are focused on a subgroup of patients with low AFP<sup>366</sup></li> </ul>								
<b>Data extracted from 12 studies:</b>								
	Study	Country	Years	Size (cm)	(n)	AFP level (ng/ml)		
						<20 n (%)	20–400 n (%)	>400 n (%)
<b>Studies rejected (12)</b>	*Sheu <i>et al.</i> , 1985 <sup>327</sup>	Taiwan	1981–1983	<2	(15)	3 (20.0%)	8 (53.3%)	4 (26.7%)
				2–5	(16)	4 (25.0%)	10 (62.5%)	2 (12.5%)
	Sheu <i>et al.</i> , 1985 <sup>367</sup>	Taiwan	1981–1983	<2	(3)	0 –	3 (100%)	0 –
				2–5	(10)	6 (60.0%)	3 (30.0%)	1 (10.0%)
				>5	(4)	1 (25.0%)	1 (25.0%)	2 (50.0%)
	*Ebara <i>et al.</i> , 1986 <sup>328</sup>	Japan	1979–1983	<2	(14)	5 (35.7%)	9 (64.3%)	0 (0.0%)
				2–5	(8)	4 (50.0%)	3 (37.5%)	1 (12.5%)
	*Cottone <i>et al.</i> , 1988 <sup>326</sup>	Italy	1988	<2	(4)	1 (25.0%)	2 (50.0%)	1 (25.0%)
				2–5	(9)	3 (33.3%)	5 (55.6%)	1 (11.1%)
				>5	(2)	0 (0.0%)	1 (50.0%)	1 (50.0%)
	Maringhini <i>et al.</i> , 1988 <sup>368</sup>	Italy	1980–1984	<5	(56)	21 (37.5%)	4 (7.1%)	31 (55.4%)
				>5	(90)	11 (12.2%)	35 (38.9%)	46 (51.1%)
Takayasu <i>et al.</i> , 1990 <sup>369</sup>	Japan	1982–1987	<2	(49)	27 (55.1%)	16 (32.7%)	6 (12.2%)	
			2–3	(48)	13 (27.1%)	25 (52.1%)	10 (20.8%)	
*Oka <i>et al.</i> , 1990 <sup>10</sup>	Japan	1983–1988	<2	(25)	8 (32.0%)	15 (60.0%)	2 (8.0%)	
			2–5	(8)	0 (0.0%)	3 (37.5%)	5 (62.5%)	
			>5	(6)	2 (33.3%)	2 (33.3%)	2 (33.3%)	
*Cottone <i>et al.</i> , 1994 <sup>287</sup>	Italy	1984–1992	<2	(12)	6 (50.0%)	6 (50.0%)	0 –	
			2–5	(18)	12 (66.7%)	6 (33.3%)	0 –	
*Zoli <i>et al.</i> , 1996 <sup>293</sup>	Italy	1989–1995	<2	(18)	8 (44.4%)	10 (55.6%)	0 –	
			2–5	(15)	5 (33.3%)	10 (66.7%)	0 –	
			>5	(1)	0 –	1 (100%)	0 –	
Oka <i>et al.</i> , 2001 <sup>370</sup>	Japan	1996–1997	<2	(126)	57 (45.2%)			
			2–5	(175)	48 (27.4%)			
			>5	(70)	16 (22.9%)			
Huo <i>et al.</i> , 2004 <sup>371</sup>	Taiwan	1996–2000	<5	(386)			78 (20.2%)	
			>5	(157)			62 (39.5%)	
Caturelli <i>et al.</i> , 2004 <sup>372</sup>	Italy	1992–2001	<2	(259)			20 (7.7%)	
<b>Source selected</b>	Pooled IPD <sup>a</sup>			<2	(88)	31 (35.2%)	50 (56.8%)	7 (8.0%)
				2–5	(74)	28 (37.8%)	37 (50.0%)	9 (12.2%)
				>5	(9)	2 (22.2%)	4 (44.4%)	3 (33.3%)

IPD, individual patient data.  
<sup>a</sup> Collected from studies identified with an asterisk.

## AFP Sensitivity

The sensitivity of AFP assay as a screening test for HCC is a function of the distribution of serum AFP levels in affected patients (i.e. the probability that an individual with HCC will have AFP above a

given threshold). The relevant thresholds defined in this study are 20 and 400 ng/ml (see the section 'Surveillance programme', p. 23).

The search identified 25 studies reporting AFP levels in patients with HCC; details are collected

in Table 24. Twelve papers were excluded at initial review, mainly because they provided insufficient detail regarding the size of tumours.

Because we were seeking to inform nine parameters that are self-evidently correlated, we were keen to rely on a single source for the estimates. Unfortunately, none of the studies identified provided a meaningful sample size for each of the subgroups of interest. However, six of the studies under consideration<sup>10,287,293,326–328</sup> reported patient-level data including AFP level and tumour size, so these data could be pooled to provide a larger sample of patients. In total, the pooled data include 171 patients (79 from Italy, 61 from Japan and 31 from Taiwan), comprising 88 small, 74 medium and nine large tumours. The resulting distribution of AFP levels according to tumour size is shown in Figure 5. Although, elsewhere, we have sought to avoid reliance on data originating in Asian populations, it was felt that, in this instance, the exclusion of studies from Japan and Taiwan would diminish an already limited sample size to an unacceptable degree. The inclusion of these cases raises the proportion of HBV-positive individuals in the pooled sample ( $55/171 = 32\%$ ) to levels that exceed those in the UK population. However, the impact of this slight imbalance is uncertain (see below).

Analysis of the pooled sample suggested that AFP levels in HCC cases may be associated with the aetiology of underlying liver disease. In particular, individuals in the sample with ALD-related cirrhosis had a higher proportion of non-secreting tumours, whereas this was comparatively unusual in those with HBV (with HCV-related cases apparently lying somewhere between the two). The observation that HCCs arising in non-viral cirrhosis are less likely to be detectable by AFP assay is consistent with some published evidence.<sup>251,288</sup> However, in contrast to the trend in the pooled sample, HCV-related tumours have been reported to be more readily AFP-detectable than those arising in HBV.<sup>251,285,288</sup> Because of uncertainties such as this, it was felt that the evidence was insufficient to justify the adoption of separate, aetiology-specific estimates in the model; however, with a broader evidence base it may be possible to tailor model inputs to reflect any variation that is present.

**Specificity**

The literature was reviewed to provide an estimate of the specificity of AFP assay as a screening test (i.e. the likelihood that a patient without HCC will have AFP levels above specified thresholds). The searches identified 17 studies providing relevant information. On preliminary review, eight of these were excluded, in five cases because the reported

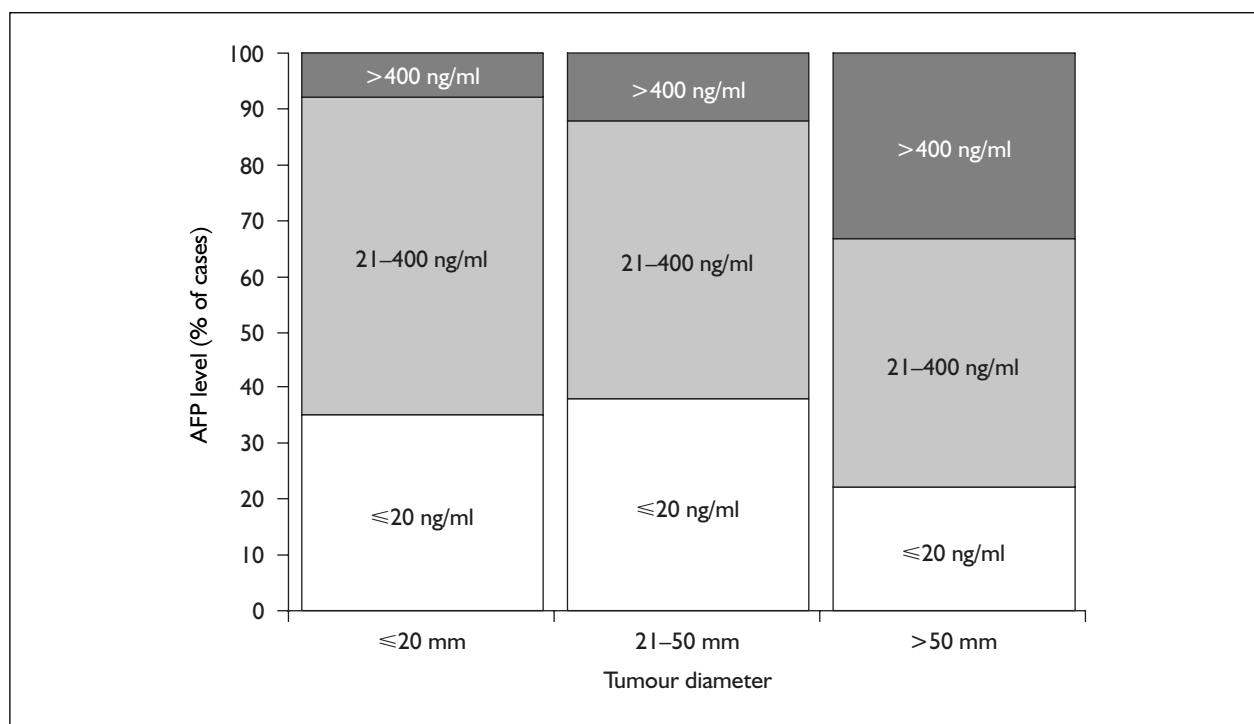


FIGURE 5 AFP level according to tumour size (data extracted from six studies reporting individual patient data<sup>10,287,293,326–328</sup>)

**TABLE 25** Selection of parameter estimates: AFP level in patients without HCC (specificity of test)

16 studies reviewed:								
Studies excluded (7):								
<ul style="list-style-type: none"> <li>• Five studies contained a substantial proportion of patients without cirrhosis<sup>40,292,361–363</sup></li> <li>• Two studies did not report results for the thresholds adopted in the model<sup>6,373</sup></li> </ul>								
Data extracted from nine studies:								
	Study	Country	Years	Population	N	AFP level (ng/ml)		
						<20	20–400	>400
<b>Studies rejected (8)</b>	Gambarin-Gelwan <i>et al.</i> , 2000 <sup>262</sup>	USA	<sup>a</sup>	Mixed	87	91%		
	Cedrone <i>et al.</i> , 2000 <sup>359</sup>	Italy	1996–1997	HBV+HCV	72	79.1%		
	Nguyen <i>et al.</i> , 2002 <sup>360</sup>	USA	1995–2001	HCV	149	79.9%	20.1%	0.0%
	Maringhini <i>et al.</i> , 1988 <sup>368</sup>	Italy	1980–1984	Mixed	217	78.8%	20.7%	0.5%
	Chalasani <i>et al.</i> , 1999 <sup>23</sup>	USA	1994–1997	Mixed	139	87%		
	Tremolda <i>et al.</i> , 1989 <sup>374</sup>	Italy	1987	Mixed	194	80%		
	Oka <i>et al.</i> , 1994 <sup>40</sup>	Japan	1985–1990	Mixed	198	76%		
	Zoli <i>et al.</i> , 1996 <sup>293</sup>	Italy	1989–1995	Mixed	130	84.6%		
<b>Study selected</b>	Trevisani <i>et al.</i> , 2001 <sup>251</sup>	Italy	1993–1996	Mixed	170	90.6%	8.8%	0.6%

populations were not confined to individuals with cirrhosis. Patients with cirrhosis have a greater probability of raised AFP levels in the absence of HCC and, accordingly, false-positive diagnoses are less frequent in patients with less advanced liver disease.<sup>359</sup> Therefore, it was judged important to exclude studies reporting patient groups whose characteristics did not match those of the simulated cohort, in this regard. The data extracted from the remaining nine studies are shown in *Table 25*.

Two main priorities informed the selection of parameters. First, we were again keen to derive the inputs from the same source, so studies that reported results for all three categories of AFP level used in the model were preferred. Secondly, we hoped to ensure that the reported populations on which we relied were not dominated by cases of postviral cirrhosis, in which non-HCC-related high levels of AFP, often coinciding with inflammatory ‘flares’, are often observed.<sup>152</sup>

Unfortunately, it was not possible to identify a single study that met both of these criteria. Of the studies that provided data for all three thresholds under consideration, the cohort presented by Nguyen and colleagues<sup>360</sup> was rejected, as it comprised HCV-related cases only. We were also reluctant to use Maringhini and co-workers’ findings,<sup>368</sup> as they report that 65% of their cases were HBV related. In addition, their paper pre-dates the identification of HCV, so they

are unable to provide information about this aetiology. Trevisani and colleagues’ case-control study<sup>251</sup> was also dominated by anti-HCV-positive individuals (70.6%). However, despite this, they had a relatively high proportion of non-secreting cases (90.6%). This figure compares quite closely to the percentage of cases below 20 ng/ml reported in the two US studies that were based on patient populations that most closely resembled the cohort under simulation (91%<sup>262</sup> and 87%<sup>23</sup>). Consequently, we chose to rely on the data reported by Trevisani and co-workers,<sup>251</sup> as it was felt that this would best approximate the specificity of AFP assay in the modelled patient group. The 95% confidence intervals of the relevant proportions were used to inform the sensitivity analyses.

Once more, there is insufficient reliable evidence available to enable separate estimates to be adopted for each aetiology of cirrhosis.

### Confirmatory imaging

The diagnostic algorithm simulated in the model specifies that patients will only receive confirmatory imaging following demonstration of a lesion on ultrasound or, in a few cases, if ultrasound has proved inconclusive in the presence of markedly elevated AFP (>400 ng/ml). Under these circumstances, it was assumed that the sensitivity of confirmatory imaging would be 100% because, although the literature shows that CT is subject to a significant false-negative rate when used in blinded, first line assessments,<sup>268,270</sup> such fallibility

**TABLE 26** Selection of parameter estimates: CT specificity

17 studies reviewed:							
<b>Studies excluded (7):</b>							
<ul style="list-style-type: none"> <li>• Five studies only report patients with HCCs<sup>214,260,375–377</sup></li> <li>• One study<sup>378</sup> reports a cohort considered in greater detail in one of the included papers<sup>325</sup></li> <li>• One study concentrated on CT arteriography<sup>379</sup></li> </ul>							
<b>Data extracted from ten studies:</b>							
	Study	Country	Years	N	HCC	False positive	Specificity
<b>Studies rejected (9)</b>	Taourel <i>et al.</i> , 1995 <sup>380</sup>	France	1992–1994	35	9	3	88.5%
	Saada <i>et al.</i> , 1997 <sup>269</sup>	UK	1993–1994	39	6	0	100.0%
	Bizollon <i>et al.</i> , 1998 <sup>381</sup>	France	1993–1995	66	15	3	94.1%
	Gambarin-Gelwan <i>et al.</i> , 2000 <sup>262</sup>	USA	<sup>a</sup>	106	19	5	94.3%
	Lim <i>et al.</i> , 2000 <sup>382</sup>	Korea	1996–1999	41	15	1	96.2%
	Rode <i>et al.</i> , 2001 <sup>261</sup>	France	1996–1997	43	13 <sup>b</sup>	3 <sup>b</sup>	94.6% <sup>b</sup>
	Libbrecht <i>et al.</i> , 2002 <sup>383</sup>	Belgium	2000–2001	16	2	3	78.6%
	Teefey <i>et al.</i> , 2003 <sup>358</sup>	USA	1996–1998	25	9	4–5 <sup>c</sup>	68.8–75.0% <sup>c</sup>
	Valls <i>et al.</i> , 2004 <sup>384</sup>	Spain	1995–2002	102	51	2	96.1%
<b>Study selected</b>	Brancatelli <i>et al.</i> , 2003 <sup>325</sup>	USA	<sup>d</sup>	430	59	38	89.8%
<sup>a</sup> “Over a 1-yr period” (study submitted 1999).							
<sup>b</sup> Lesion-by-lesion calculation (patient-specific data not reported).							
<sup>c</sup> Data for two independent reviewers.							
<sup>d</sup> “Over a 30-month period” (study submitted 2002).							

should not be apparent when the technique is adopted in a second line, confirmatory context.

Consequently, the only concern was to identify an estimate of the specificity of CT (that is, its ability to avoid false-positive results in cases where no HCC is present). Again, the search was confined to studies that used explant pathology as a reference standard. Seventeen such studies were identified, details of which are collected in *Table 26*.

Of the eight studies considered in detail, Brancatelli and colleagues’ series<sup>325</sup> was readily chosen, as it clearly provides the strongest available evidence: it is recent, has a much larger sample size than any of the other papers, and was published as a dedicated investigation into false-positive results in CT diagnosis of HCC. These strengths substantially outweigh any increased applicability in the UK-specific data available in Saada and co-workers’ paper,<sup>269</sup> as this study is quite old and based on a very small sample.

## Mortality

### Background (all-cause) mortality

The interim life tables (2002–2004) for England and Wales published by the Government Actuary’s Department ([http://www.gad.gov.uk/Life\\_Tables/Interim\\_life\\_tables.htm](http://www.gad.gov.uk/Life_Tables/Interim_life_tables.htm)) were used. These data are

based on the mid-year population estimates for 2002, 2003 and 2004 and corresponding data on births, infant deaths and deaths by individual ages from these years. Data for males and females are presented separately.

### Excess mortality associated with a diagnosis of compensated cirrhosis

Evidence from several studies suggests that there is no excess mortality associated with a diagnosis of compensated cirrhosis. Patients with compensated cirrhosis are therefore subject to the background mortality rate only.

### Excess mortality associated with a diagnosis of decompensated cirrhosis

Ten studies were found reporting excess mortality associated with a diagnosis of decompensated cirrhosis (*Table 27*). On initial review, three papers were excluded, predominantly because they were confined to specific symptoms of decompensation.

The evidence base provided three reliable estimates for HBV and three for HCV. Because there was no reason to prefer the evidence from any of these studies, the middle of each set of three values was used in the base case, with the upper and lower estimates used to define the range adopted in sensitivity analyses.

**TABLE 27** Selection of parameter estimates: excess mortality associated with decompensated cirrhosis

Ten studies reviewed:								
<b>Studies excluded (3):</b>		<ul style="list-style-type: none"> <li>• Outcomes of interest too wide ranging to correspond to the definition of decompensation<sup>355</sup></li> <li>• Outcome of interest too specific to correspond to the definition of decompensation<sup>62</sup></li> <li>• Insufficient follow-up<sup>50</sup></li> </ul>						
<b>Data extracted from seven studies:</b>								
	<b>Study</b>	<b>Country</b>	<b>Years</b>	<b>Aetiology</b>	<b>N</b>	<b>Survival</b>	<b>Equiv. monthly mortality rate</b>	<b>Equiv. annual mortality rate</b>
<b>Studies rejected</b>	D'Amico <i>et al.</i> , 1986 <sup>52</sup>	Italy	1974–1980	27–31% ALD <sup>a</sup> 19–24% HBV <sup>a</sup> ?HCV <sup>b</sup>	720	60% at 1 year 21% at 6 years	4.17% 2.14%	40.00% 22.90%
	Ginés <i>et al.</i> , 1987 <sup>51</sup>	Spain	1968–1980	41.6% ALD <sup>c</sup> 8.5% HBV <sup>c</sup> ?HCV <sup>b</sup>	121	c.62% at 1 year <sup>d</sup> c.36% at 3 years <sup>d</sup> c.17% at 5 years <sup>d</sup> Median 19.2 mo	3.91% 2.80% 2.91% 3.55%	38.00% 28.86% 29.84% 35.16%
	de Jongh <i>et al.</i> , 1992 <sup>69</sup>	Netherlands	1970–1990	HBV	21	70% at 1 year 35% at 3 years 14% at 5 years	2.93% 2.87% 3.22%	30.00% 29.53% 32.51%
	Fattovich <i>et al.</i> , 1995 <sup>98</sup>	Europee	1973–1991	HBV	88	c.59% at 1 year <sup>d</sup> c.39% at 3 years <sup>d</sup> 35% at 5 years	4.30% 2.58% 1.73%	41.00% 26.94% 18.93%
	Fattovich <i>et al.</i> , 2002 <sup>67</sup>	Europee	1982–1992	HCV	49	82% at 1 year 60% at 3 years 47% at 5 years	1.64% 1.41% 1.25%	18.00% 15.66% 14.01%
	Planas <i>et al.</i> , 2004 <sup>385</sup>	Spain	1998–2001	HCV	200	c.83% at 1 year <sup>d</sup> c.71% at 3 years <sup>d</sup> 50.8% at 5 years	1.54% 0.95% 1.12%	17.00% 10.79% 12.66%
<b>Studies selected</b>	Fattovich <i>et al.</i> , 2002 <sup>67</sup>	Europe <sup>e</sup>	1982–1992	HBV	33	71% at 1 year 40% at 3 years 28% at 5 years	2.81% 2.51% 2.10%	29.00% 26.32% 22.47%
	Fattovich <i>et al.</i> , 1997 <sup>64</sup>	Europe <sup>e</sup>	1982–1992	HCV	65	c.82% at 1 year <sup>d</sup> c.59% at 3 years <sup>d</sup> 50% at 5 years	1.64% 1.46% 1.15%	18.00% 16.13% 12.95%

<sup>a</sup> Range among retrospectively and prospectively enrolled patients.  
<sup>b</sup> Study pre-dates identification of HCV.  
<sup>c</sup> Proportion only reported for whole cohort ( $n = 293$ ), which includes patients with compensated cirrhosis.  
<sup>d</sup> Estimated from published Kaplan–Meier graph; precise figures not specified.  
<sup>e</sup> Nine centres in Italy, Denmark, France, Greece, The Netherlands, Portugal and Spain.

No published evidence was found to inform the estimate of excess mortality associated with ALD-related decompensated cirrhosis. In the absence of aetiology-specific data, an average of the chosen HBV and HCV values (17.7% per annum) was used as the base-case estimate, with sensitivity analyses conducted over the full range of values reported for either hepatitis aetiology (12.7–32.5%).

#### **Excess mortality associated with surgically untreatable HCC**

In order to estimate the excess mortality associated with surgically untreatable large HCC the mortality

rates following transarterial chemoembolisation and best supportive care were considered, as these are the treatment pathways most associated with large tumours. The sources and data are described in more detail below. The overall mortality rate for patients with untreatable large HCC was calculated using a weighted average in which one-third of patients receive TACE and two-thirds receive best supportive care only.

#### **Mortality following TACE**

In total, 26 studies were identified reporting long-term survival data of TACE; details are collected

**TABLE 28** Selection of parameter estimates: mortality following transarterial chemoembolisation

26 studies reviewed:						
<b>Studies excluded (19):</b>						
<ul style="list-style-type: none"> <li>• 12 Asian studies<sup>387–398</sup></li> <li>• Two insufficient sample size (<math>n &lt; 30</math>)<sup>399,400</sup></li> <li>• Two series reported insufficiently current experience (<math>&gt; 15</math> years ago)<sup>401</sup></li> <li>• One only considered TACE in conjunction with tamoxifen<sup>402</sup></li> <li>• One only reported subgroups; no data for whole cohort<sup>386</sup></li> <li>• One included an unspecified proportion of non-cirrhotic patients, and excluded all patients with decompensated cirrhosis<sup>403</sup></li> </ul>						
<b>Data extracted from seven studies:</b>						
	Study	Country	Years	N	Survival	Monthly rate
<b>Studies rejected (6)</b>	Saccheri <i>et al.</i> , 2002 <sup>404</sup>	Italy	1993–1998	56	32% at 3 years	0.03116
	Llovet <i>et al.</i> , 2002 <sup>405</sup>	Spain	1996–2000	40	29% at 3 years	0.03380
	Greten <i>et al.</i> , 2005 <sup>83</sup>	Germany	1998–2004	49	29% at 3 years Median survival 16 months	0.03380 0.04240
	Llado <i>et al.</i> , 2000 <sup>406</sup>	Spain	1990–1996	143	19% at 3 years Median survival c. 15 months	0.04508 0.04516
	GETCH, 1995 <sup>407</sup>	France	1990–1992	50	26% at 2 years c. 14% at 3 years Median survival c. 18 months	0.05458 0.05315 0.03778
	Rose <i>et al.</i> , 1999 <sup>408</sup>	USA	1991–1998	39	11% at 3 years Median survival 9.2 months	0.05947 0.07257
<b>Study selected</b>	Shah <i>et al.</i> , 1998 <sup>409</sup>	UK	1992–1997	37	14.8% at 3 years	0.05169

in Table 28. Nineteen papers were excluded at initial review. Two papers reporting early experience of TACE from the 1980s were excluded, as they were unlikely to provide data that would fit the present-day perspective of the model.

Three of the studies under consideration were felt likely to overestimate the efficacy of TACE, from the perspective of the model. Llovet and colleagues' estimate<sup>405</sup> derives from an RCT with strict patient eligibility criteria, meaning that their mortality rate is very likely to reflect a younger, fitter cohort than the general population under simulation. In a similar way, Saccheri and colleagues' 2002 case series<sup>404</sup> would probably have limited applicability to the model, since these investigators explicitly excluded older patients, and those with complicated tumours and/or advanced liver disease. The treatment algorithm followed by Greten and co-workers<sup>83</sup> specified TACE as first line therapy of choice for all unresectable patients; accordingly, their results are likely to overestimate the efficacy that this approach would be likely to have in the simulated cohort, in which RFA and PEI are used preferentially.

Notably, the four remaining studies reported relatively similar outcomes, with 3-year survival rates of 11–19%. Both because the point estimate of 14.8% represented a good average of this range and because it was based on UK-specific experience, we decided to adopt the survival rate provided by Shah and colleagues' series.<sup>409</sup> Although the sample size of 37 on which this result is based falls below the lower limit applied in some of the other parameter-choice criteria, it was felt that its comparability with the other, larger series could be seen as evidence of a relatively robust finding.

**Mortality with best supportive care**

To provide a parameter estimate for mortality arising from HCCs that are not amenable to any form of life-extending therapy, 13 series of untreated HCC were reviewed (Table 29). In general, these series represented the control arm in the analysis of an active treatment, or were derived from reviews (mostly retrospective) of individual units' experience with all treatment strategies for HCC.

The survival rate published by Llovet and co-workers from the Barcelona clinic<sup>143</sup> is, in relative

**TABLE 29** Selection of parameter estimates: mortality with best supportive care

13 studies reviewed:						
<b>Studies excluded (9):</b>						
<ul style="list-style-type: none"> <li>• Four Asian studies<sup>388,394,395,410</sup></li> <li>• Five insufficient sample size (<math>n &lt; 50</math>)<sup>76,405,407,408,411</sup></li> </ul>						
<b>Data extracted from four studies:</b>						
	Study	Country	Years	N	Survival	Monthly rate
<b>Studies rejected (3)</b>	Llovet <i>et al.</i> , 1999 <sup>143</sup>	Spain	1992–1994	102	28% at 3 years Median survival 17 months	0.03474 0.03995
	Buscarini <i>et al.</i> , 1996 <sup>88</sup>	Italy	1989–1993	127	16% at 2 years c.10% at 3 years Median survival c.7 months	0.07352 0.06196 0.09428
	Ryder <i>et al.</i> , 1996 <sup>401</sup>	UK	1988–1991	118	Median survival 2.3 months	0.26019
<b>Study selected</b>	Greten <i>et al.</i> , 2005 <sup>83</sup>	Germany	1998–2004	194	2% at 3 years Median survival 6 months	0.10297 0.10910

terms, extremely high. This is doubtless because their paper is based on the amalgamated control arms of two RCTs<sup>412,413</sup> that featured stringent inclusion criteria, such that older patients with more advanced disease were excluded from analysis. The consequent inflation of apparent survival, which has been noted by others,<sup>414</sup> makes this study an unsuitable source of parameters for the model.

Conversely, it was felt that the one UK study on the shortlist<sup>401</sup> represented an unnecessarily gloomy prognosis, probably because the experience it reports is nearly 20 years old. Although some improvement in symptomatic management will have contributed to lengthening survival times over this period, we suspect that Ryder and colleagues' estimate appears pessimistic from today's perspective largely as a result of the extra lead-time provided by HCC surveillance (i.e. 'lead-time bias': patients being identified and monitored from an earlier stage in their terminal deterioration, thereby effectively increasing apparent survival). Accordingly, it was decided that a more up-to-date estimate would better inform the treatment pathways being simulated by the model.

There are some clear similarities between the remaining two studies: both papers are retrospective reports of a single European unit's experience in the management of HCC and, especially as regards median survival estimates of 6 and 7 months, they also present similar results. Ultimately, the German study of Greten and co-workers<sup>83</sup> was adopted, for three main reasons:

(1) the German population more closely resembles the UK than the Italian, especially as regards the relative contributions of the various causes of cirrhosis; (2) the experience reported is more recent; and (3) a more extensive treatment programme had been adopted in the German unit, with the untreated patients representing 49.9% of the whole cohort, compared with 70.2% of the patients reported by Buscarini and colleagues,<sup>88</sup> and it was felt that this was a more accurate reflection of the treatment algorithm being simulated (see the section 'Treatment', p. 25).

#### **Mortality following resection: perioperative and long-term**

In total, 35 papers were identified presenting detailed results of resective surgery for HCC, details of which are shown in *Table 30*. All but three of these studies were excluded from consideration. Since, according to the assumptions of the model, patients with HCCs greater than 5 cm in diameter would be rejected as candidates for surgery, five studies that featured a substantial proportion (>30%) of such cases were excluded.

Wayne and colleagues' analysis<sup>431</sup> is based on a large sample drawn from an international cooperative group. However, on close scrutiny, it was noted that the data presented combine patients with precirrhotic severe fibrosis with cirrhotic cases. There was also concern that their results, which represent experience stretching back to 1980, might underestimate the efficacy of present-day surgical standards. Similarly, the cohort reported by Ercolani and co-workers<sup>174</sup> includes some operations undertaken more than

**TABLE 30** Selection of parameter estimates: mortality following hepatic resection

35 studies reviewed:						
<b>Studies excluded (32):</b>						
<ul style="list-style-type: none"> <li>• 12 Asian studies<sup>176,178,179,190,193,415–421</sup></li> <li>• 11 insufficient sample size (<math>n &lt; 50</math>)<sup>171,172,186,205,411,422–427</sup></li> <li>• Four included a substantial proportion of non-cirrhotic cases<sup>155,165,428,429</sup></li> <li>• Five included a substantial proportion of large tumours (&gt;5 cm)<sup>166,173,188,213,430</sup></li> </ul>						
<b>Data extracted from three studies:</b>						
	Study	Country	Years	N	Survival	Monthly rate
<b>Studies rejected (2)</b>	Wayne <i>et al.</i> , 2002 <sup>431</sup>	USA, China, France, Japan	1980–1998	182	(Periop. mortality 6.1% <sup>a</sup> ) c.79% at 1 year <sup>b</sup> c.54% at 3 years <sup>b</sup> c.36% at 5 years <sup>b</sup> c.13% at 10 years <sup>b</sup> Median survival 45.6 months	0.01945 0.01697 0.01688 0.01686 0.01509
	Ercolani <i>et al.</i> , 2003 <sup>174</sup>	Italy	1983–1999	285	(Periop. mortality excluded) 83% at 1 year 62.8% at 3 years 42.5% at 5 years	0.01541 0.01284 0.01416
<b>Study selected</b>	Llovet <i>et al.</i> , 1999 <sup>216</sup>	Spain	1989–1997	77	96.1% at 3 months 85% at 1 year 62% at 3 years 51% at 5 years Median survival 65 months	0.01316 0.01345 0.01319 0.01116 0.01061
<sup>a</sup> Perioperative mortality across all stages of liver disease (no cirrhosis-specific numbers available).						
<sup>b</sup> Estimated from published Kaplan–Meier graph; precise figures not specified.						

20 years ago. It also includes 19% of patients with tumours larger than 5 cm in diameter. Both of these features make it likely that these results are inferior to those that might be expected in the simulated cohort of current patients with cirrhosis. A bias in the opposite direction is introduced by the fact that cases of perioperative (30-day) mortality were excluded from analysis.

The other paper considered reports experience at the Barcelona unit in 1989–1997.<sup>216</sup> The sample is quite small ( $n = 77$ ) compared with some of the other papers reviewed and, once more, some patients had tumours larger than 5 cm in diameter, although the proportion (7.8%) is small. In addition, survival rates appeared quite high in comparison to the other papers under review; however, as a relatively recent series with selective inclusion criteria, this may well be more reflective of the experience modelled here. On a balance of these considerations, it was concluded that this study provided the most reliable and applicable data available for the model.

**Mortality rate following liver transplant**

To define short- and long-term mortality rates following OLT, this study used data supplied

directly by UK Transplant from the National Transplant Database maintained on behalf of the transplant services in the UK and Republic of Ireland (Table 31).

The 90 day and 1-year outcomes are based on the most recent cohort in the database, who underwent OLT in 2000–2004. Because 5-year follow-up is not available for this cohort, data from the previous 5 years (1996–2000) were used. Although relying on two separate cohorts introduces additional heterogeneity to the data set, it was felt that the disadvantages of doing so were outweighed by the advantage of using the most current data available for 90-day and 1-year outcomes.

**Waiting list for liver transplantation**

UK Transplant’s National Transplant Database was also used to define waiting times for OLT (Table 32).

It should be noted that these data categorise patients according to the primary liver disease specified at the time of listing; this has the important implication that the ‘HCC’ category represents a minority of patients with tumours on



**TABLE 31** Selection of parameter estimates: mortality following liver transplant

Year of transplant	Liver disease at OLT	No. at risk on day 0	% Patient survival (95% CI)		
			90 day	1 year	5 year
2000–2004	HCC+HCV	136	92.6 (88.2, 97.0)	87.6 (81.9, 93.3)	
	HCC+HBV	47	85.0 (74.7, 95.3)	78.0 (65.9, 90.1)	
	HCC+ALD	50	94.0 (87.4, 100.0)	92.0 (84.5, 99.5)	
1996–2000	HCC+HCV	99	86.9 (80.2, 93.5)	78.4 (70.2, 86.6)	55.8 (41.0, 70.6)
	HCC+HBV	44	93.1 (85.5, 100.0)	81.1 (69.4, 93.0)	68.5 (54.3, 82.8)
	HCC+ALD	37	94.6 (87.3, 100.0)	86.3 (75.1, 97.4)	54.7 (38.2, 71.3)

Patient survival after first adult elective orthotopic liver only transplant in the UK using livers from deceased heartbeating donors, for patients with HCC and another liver disease (HCV or HBV or ALD) recorded at transplantation, 1 January 1996 to 31 December 2004.  
Patients with missing follow-up data are excluded.  
The HCC+HCV, HCC+HBV and HCC+ALD groups are not mutually exclusive.

**TABLE 32** Selection of parameter estimates: time on waiting list for liver transplantation

Primary liver disease at registration	Registrations		Outcome				Median waiting time to transplant <sup>c</sup> (days) (95% CI)	
	N	N (%)	Transplanted	Died	Removed <sup>a</sup>	Removed <sup>b</sup>		Waiting
			N (%)	N (%)	N (%)	N (%)		N (%)
HCC	79	71 (90)	5 (6)	0 (0)	3 (4)	0 (0)	39 (29, 45)	
Other	2661	2188 (82)	238 (9)	93 (3)	101 (4)	41 (2)	73 (69, 78)	
Overall	2740	2259 (82)	243 (9)	93 (3)	104 (4)	41 (1)	72 (68, 76)	

Outcome of group 1 elective adult registrations on the UK liver transplant list for the registration period 1 January 2000 to 31 December 2004 (as at 10 October 2005). Data provided by UK Transplant.  
<sup>a</sup> Removal due to 'condition deteriorated'.  
<sup>b</sup> Removal for reasons other than 'condition deteriorated'.  
<sup>c</sup> Calculated using the Kaplan–Meier method.

the list (in fact, UK Transplant data show that 282 patients with a primary *or* secondary diagnosis of HCC received OLTs during this period). Because of this ambiguity, and because of the difficulty in specifying a common protocol for waiting list prioritisation (see the section 'Treatment', p. 25), the overall average data were used to define the waiting times for patients with all indications for OLT.

If, as UK Transplant's figures suggest, there is at least a subgroup of patients with HCC who receive *de facto* prioritisation on the waiting list, the model may slightly underestimate the effectiveness of OLT, as an intervention, for these individuals. This would also mean that there would be a very small extra advantage to surveillance, because patients with known HCCs will have a better chance of receiving OLT than those with occult tumours in the setting of decompensation. This

raises the further complication that an assessment of the cost-effectiveness of surveillance for HCC among those already awaiting OLT for liver failure would be demanded. Taking these considerations into account, we were not prepared to implement very complicated modelling algorithms to capture a small difference, on which the evidence is uncertain.

### Selection of parameters: resources

Costing was conducted using a mixed bottom-up and top-down costing approach from an NHS perspective. An NHS perspective ignores some costs to patients and their families that would inevitably follow from taking part in the surveillance programme; however, there are no reliable data on what these would be.

The source of cost estimates for each of the resources considered, together with the unit cost used in the base case and the range of values used in the sensitivity analyses and a justification for the estimates used, is provided below.

**Unit costs of surveillance programme, diagnostic tests and treatments**

**Administration of the surveillance programme**

We initially considered including the following additional resources that might be needed to operate a comprehensive surveillance programme in NHS liver units:

- extra clerical staff time (entering patient details, updating attendance records)
- telephone or postal costs to notify patients of next appointment
- materials development (e.g. information leaflet).

Few data are available to accurately estimate such costs. Also, on a per-patient basis it is likely that these costs will mostly be subsumed within the existing running costs of a hepatology specialist outpatient clinic. Therefore, no such costs were assumed in the analysis.

**AFP test**

In the NHS National Schedule of Reference Costs (NSRC) 2004<sup>432</sup> the cost of a biochemistry test (TPATH table in NSRC 2004) is cited as £1.15. This is an average figure for any biochemistry test; enquiries by this group indicate that the standard cost of an AFP test may be greater than this.

Data obtained from a small sample (October 2005) of NHS trust clinical biochemistry departments suggests a cost of between £2.70 and £6.40 (individual costs were £2.70, £4, £5 and £6.40). In the mild hepatitis C trial and cost-effectiveness analysis,<sup>433</sup> hospitals in London, Newcastle and Southampton provided estimates of the cost of an AFP test as £5.30, £4.50 and £8.30, respectively (2002/03 costs). Therefore, the base-case cost of an

AFP test was set at £4, and varied between £2 and £8 in the sensitivity analysis (Table 33). It was assumed that the cost of obtaining the blood sample for the AFP test was so small as to be negligible.

**Liver ultrasound**

In the NHS NSRC 2004<sup>432</sup> the cost of an ‘other ultrasound’ (TRADIO table in NSRC 2004) is £32. Again, this is an average figure for ultrasound examinations and enquiries suggest that the standard cost of a liver ultrasound may be higher.

In the mild chronic hepatitis C trial and cost-effectiveness analysis<sup>433</sup> the procedure costs for a liver ultrasound examination were based on site visits, estimated staff time involved and consumables used, and included an allocation for overheads and capital (based on a previous study). The estimated costs of a liver ultrasound in the three hospitals were £44, £62 and £108, respectively (2002/03 costs).

Given these variable data, the cost of a liver ultrasound in the base case was set at £50, and the cost was varied widely between £26 and £100 in the sensitivity analysis (Table 34).

**Confirmatory imaging (CT or MRI)**

The NHS NSRC 2004<sup>432</sup> provides a global cost estimate for all CT and MRI scans regardless of anatomical focus. Therefore, for consistency with the sources used for cost estimates of AFP tests and liver ultrasound, the costs described in the mild chronic hepatitis C trial and cost-effectiveness analysis<sup>433</sup> were used. These are shown in Table 35.

In the base case, all confirmatory imaging is by CT scan. A cost estimate of £110 per CT scan was used in the base case, and varied between £50 and £130 in the sensitivity analysis. This base-case assumption and range reflect the substantially lower cost of £49 from the NHS NSRC.<sup>432</sup>

**TABLE 33** Selection of parameter estimates: cost estimates for AFP tests

Resource	Unit cost (£)	Unit	Lower value	Upper value	Source
AFP test	4	per test	2	8	Various NHS trust clinical biochemistry departments, plus estimates from hospitals in London, Southampton and Newcastle included in the Mild Hepatitis C Trial <sup>433</sup>

**TABLE 34** Selection of parameter estimates: unit costs for liver ultrasound

Resource	Unit cost (£)	Unit	Lower value	Upper value	Source
Liver ultrasound scan	50 <sup>a</sup>	per scan	26 <sup>a</sup>	100	Data from NSRC 2004 <sup>432</sup> and estimates from hospitals in London, Southampton and Newcastle included in the mild hepatitis C trial <sup>433</sup>

<sup>a</sup> For comparison, the NSRC 2004<sup>432</sup> “direct access” cost of an “other ultrasound” scan (Korner radiology band B3) is £32 [interquartile range (IQR) £26–39].

**TABLE 35** Selection of parameter estimates: unit costs for confirmatory imaging

Resource	From mild hepatitis C trial			Values chosen for model		
	London	Newcastle	Southampton	Base case	Lower value	Upper value
CT Abdomen	£111	£136	£111	£110	£50 <sup>a</sup>	£130 <sup>c</sup>
MRI Liver	£240	£193	£185	£200 <sup>b</sup>	£180 <sup>c</sup>	£400 <sup>c</sup>

<sup>a</sup> For comparison, the NSRC 2004<sup>432</sup> ‘direct access’ cost of a CT scan (Korner radiology band C5) is £49.  
<sup>b</sup> For comparison, the NSRC 2004<sup>432</sup> ‘direct access’ cost of an MRI scan is £224 (IQR £194–465).  
<sup>c</sup> Based on the NSRC 2004<sup>432</sup> IQR for the cost of CT and MRI scans.

**TABLE 36** Selection of parameter estimates: cost estimates for liver transplantation

Resource	Unit cost (£)	Unit	Lower value	Upper value	Source
Liver transplant	21,800	per operation	16,700	31,800	NSRC 2004 national average cost for liver transplant <sup>432</sup>

Other confirmatory imaging protocols were explored in sensitivity analyses. It was assumed that MRI or CT scan(s) performed during the assessment process for treatment are included in the inpatient cost of a liver transplants, resections and other treatments.

#### **Liver transplantation and resection (including repeat resections)**

The NHS NSRC 2004<sup>432</sup> provides an average unit cost for a liver transplant of £21,800. A large, recent study of the cost-effectiveness of liver transplantation in England and Wales reports other figures for the cost of the ‘transplant phase’ for all elective transplant patients (£29,957)<sup>434</sup> and for elective transplant patients with hepatitis C (£27,330;  $n = 67$ ) (as cited in Wright<sup>433</sup>). Based on these figures, and the interquartile range of cost estimates within the NHS NSRC 2004, a cost estimate for liver transplant of £21,800 was used in the base case, and the estimate varied from

£16,700 to £31,800 in the sensitivity analysis (Table 36).

There are two potentially appropriate cost estimates for liver resection in the NHS NSRC 2004:<sup>432</sup> ‘Liver – complex procedures’ and ‘Liver – very major procedures’. It was assumed that ‘Liver – complex procedures’ would encompass most resection procedures that aim to remove HCC-affected lobes from cirrhotic livers. Example procedures from this category include right and left hemihepatectomy, resection of segment of liver and partial excision of liver. Therefore, a cost estimate for liver resection in the base case of £5400 was used, and the estimate varied from £1500 to £6000 in the sensitivity analysis (Table 37). (Although the 2004 national average unit cost of a complex liver procedure was £5396, the interquartile range across the ten UK liver transplant centres was £1484 to £5104.) Note also that the average unit cost of procedures within the

**TABLE 37** Selection of parameter estimates: cost estimates for liver resection

Resource	Unit cost (£)	Unit	Lower value	Upper value	Source
Liver resection	5400	per operation	1500	6000	NSRC 2004 national average cost for liver procedures <sup>432</sup>

**TABLE 38** Selection of parameter estimates: cost estimates for outpatient appointment

Resource	Unit cost (£)	Unit	Lower value	Upper value	Source
Liver transplant	101	per appointment	72	133	NSRC 2004 national average cost for medical gastroenterology follow-up visits <sup>432</sup>

**TABLE 39** Selection of parameter estimates: mean annual costs (£) by disease state

	2002/03 <sup>a</sup>		Inflated to 2003/04 prices <sup>b</sup>
	Mean	SD	Mean
Compensated cirrhosis (n = 115)	1138	2479	1171
Decompensated cirrhosis (n = 40)	9120	9610	9385

<sup>a</sup> From mild hepatitis C trial.<sup>433</sup>  
<sup>b</sup> Using inflation indices for Hospital and Community Health Services (Pay and Prices) from Unit Costs of Health and Social Care 2004<sup>435,436</sup>

category 'Liver – very major procedures' is £2498, which still lies within the broad range of values included in the sensitivity analysis.

**Gastroenterology outpatient appointment**

The assumed process of discovering false-positive surveillance results includes two hospital outpatient appointments, at a unit cost of £101 each (Table 38).

**Annual medical costs of disease states  
Compensated cirrhosis, decompensated cirrhosis and HCC**

The medical costs of patients with compensated cirrhosis and decompensated cirrhosis were derived from a large study of the cost-effectiveness of liver transplantation in the UK.<sup>433,434</sup> As part of this study, all patients listed for liver transplantation at the six UK liver transplant centres between 1995 and 1996 were followed while waiting for their transplant and for 2 years following postoperative discharge. Mean annual medical costs before transplantation were calculated and presented by stage of cirrhosis. Using the inflation indices for Hospital and Community Health Services (Pay and Prices) provided in Unit Costs for Health and

Social Care 2004,<sup>435,436</sup> this study used an annual cost estimate for compensated cirrhosis of £1171 and for decompensated cirrhosis of £9385. Further details are provided in Table 39.

The medical costs of patients with a diagnosis of HCC are dependent on whether a patient is deemed suitable for surgical intervention or not. Resource use and costs are detailed below.

**Undiagnosed HCC**

The annual medical cost of undiagnosed (occult) HCC is assumed to be the same as the annual medical cost for the underlying level of cirrhosis.

**Transplant waiting list**

In the mild hepatitis C clinical trial and cost-effectiveness study,<sup>433</sup> the 20 patients with a diagnosis of HCC used an excess of resources over and above what might have been expected from their underlying stage of liver cirrhosis. Therefore, an increased cost and resource use associated with patients on the liver transplant waiting list with HCC was assumed, by calculating a cost increment that is added to the medical costs associated with the underlying level of cirrhosis.

**TABLE 40** Selection of parameter estimates: cost estimate for the additional cost of a patient with HCC on the waiting list for a liver transplant

	Excess <sup>a</sup>	Unit cost (2002/03) (£)	Unit cost (inflated to 2003/04 prices <sup>b</sup> ) (£)	Annual excess cost (inflated to 2003/04 prices <sup>b</sup> ) (£)
Inpatient days: liver unit	+1	198	203	203
Inpatient days: general	+7	136	140	982
Outpatient visits	+0.5	18	19	9
Hepatic angiographies	+0.5	322	331	166
Liver biopsies	+0.15	249	256	38
Endoscopies	-1	164	169	-169
Total				1567

<sup>a</sup> Derived from Table 33 in mild hepatitis C clinical trial and cost-effectiveness analysis.<sup>433</sup>

<sup>b</sup> Using inflation indices for Hospital and Community Health Services (Pay and Prices) from Unit Costs of Health and Social Care 2004.<sup>435,436</sup>

Estimates of the differences in the number of inpatient days, hepatic angiographies, liver biopsies, outpatient visits and endoscopies that were carried out among the 20 hepatitis C patients with HCC are shown in *Table 40*. Following inflation of the unit costs with appropriate inflation indices, the total additional annual cost for a patient with HCC on the waiting list for a liver transplant is £1230. This was varied between £615 and £2460 in the sensitivity analyses.

Apart from these costs, the decision was made to include no additional costs due to time spent waiting for a transplant. In England and Wales, for the majority of patients on the liver transplant waiting list there are few specific tests or hospital outpatient appointments that are specific to being on the transplant waiting list (as opposed to tests or appointments that are related to their underlying disease) [Longworth L, health economist on the Department of Health's Cost-Effectiveness of Liver Transplantation (CELT) study: personal communication, 11 November 2005]. The Department of Health's economic evaluation of liver transplantation in England and Wales collected costs specific to the pretransplant 'candidacy phase' (between date of listing and date of admission for the transplant operation).<sup>433,434</sup> However, there was no distinction between costs associated with the treatment of their underlying disease or symptoms, and those associated with monitoring in preparation for the transplantation.

#### Postresection

The annual medical cost assigned to patients following hepatic resection is assumed to be the same as the annual medical cost for the underlying level of cirrhosis, plus an amount to

reflect HCC recurrence and treatment following resection.

The rates of HCC recurrence and likely treatment were taken from the same study as the postresection survival rate.<sup>216</sup> The probability of HCC recurrence 5 years after resection was 70%, which is equivalent to a monthly probability of recurrence of 2%. Of these, one-quarter were assumed to be treated curatively (approximately one-third by a further resection, one-third by liver transplant and one-third by palliative treatments). Therefore, a quarter of 2% of the relevant costs implies a mean additional monthly cost due to HCC recurrence of £46 (lower £31; upper £65).

#### Post-transplantation

The Department of Health study into the cost-effectiveness of liver transplantation in England and Wales followed patients for 2 years post-transplantation, including their resource use during this time. The costs of care in this study (2002/03 costs) are: £9458 (SD £20,856) for months 0–12 post-transplantation and £1385 (SD £2906) for months 13–24 post-transplantation. Taking into account inflation to 2004, these costs are £9733 and £1425, respectively (as cited in Table 35 of Wright and colleagues' subanalysis of those transplantations for people with hepatitis C<sup>433</sup>).

A small amount was added to reflect HCC recurrence and treatment following transplantation. The probability of HCC recurrence 5 years after transplantation is 25% or less, which approximates to a monthly probability of 0.005. As with postresection treatment of recurrent HCC, it was assumed that only one-

quarter would be treated curatively (approximately one-third by a further resection, one-third by liver transplant and one-third by palliative treatments). Therefore, a quarter of 0.5% of the relevant costs implies a mean additional monthly cost due to HCC recurrence of £12 (lower £8; upper £16). Relative to the other post-transplant costs (£9733 and £1425 annually) these are unlikely to make a substantial difference to the results, but they are included in the analysis for completeness.

**Surgically untreatable HCC**

Patients diagnosed with HCC that is deemed surgically untreatable may receive palliative treatment. Based on information sought from clinical expert advisors to the project, it was simply assumed that one-third of patients with small- and medium-sized tumours receive PEI and one-third receive RFA. One-third of patients with large tumours receive treatment with TACE in addition to best supportive care. The cost estimates for each of these treatment options are shown in Table 41.

**Event-related costs**

**False-positive diagnosis**

For the very small proportions of patients who experience a false-positive diagnosis, it was

assumed that their discovery would involve an additional CT scan, an additional MRI scan and two additional outpatient visits. Together, these amount to £512 in the base case (range for sensitivity analyses £374–796). The sources of the unit costs for each of these have been described above.

**Symptomatic/incidental diagnosis**

It was assumed that confirming a symptomatic or an incidental HCC diagnosis (i.e. outside the surveillance programme) would entail one AFP test, one liver ultrasound and one CT scan. Together, these amount to £164 in the base case (range for sensitivity analyses £78–238). The sources of the unit costs for each of these have been described above. Although such symptomatic or incidental diagnoses may not always involve all three of these tests, we do not believe that this will overestimate the cost of no surveillance because some of these would probably involve a more costly MRI scan instead of the CT scan.

**Selection of parameters: utilities**

The decision model requires utility values for a number of disease states. Initially, the following

**TABLE 41** Selection of parameter estimates: cost of palliative treatments used in patients with surgically untreatable HCC

Resource	Unit cost (£)	Unit	Lower value (£)	Upper value (£)	Source
TACE	537	per procedure	268	1074	Estimates from hospitals in London, Southampton and Newcastle included in the Mild HCV Trial <sup>433</sup>
PEI	381	per procedure	190	762	Estimates from hospitals in London, Southampton and Newcastle included in the Mild HCV Trial <sup>433</sup>
RFA	754	per procedure	377	1508	Estimates from hospitals in London, Southampton and Newcastle included in the Mild HCV Trial <sup>433</sup>
Best supportive care (with untreatable HCC)	1230	Extra per year <sup>a</sup>	615	2460	Mild HCV clinical trial and cost-effectiveness analysis <sup>433</sup>
Surgically untreatable HCC <sub>S</sub> and HCC <sub>M</sub>	1619 <sup>b</sup>	Extra per year <sup>a</sup>	809	3237	As above, plus stated assumptions regarding proportions receiving PEI and RFA
Surgically untreatable HCC <sub>L</sub>	177 <sup>c</sup>	Extra per year <sup>d</sup>	88	354	As above, plus stated assumptions regarding proportion receiving TACE

<sup>a</sup> In addition to the medical costs associated with the underlying level of cirrhosis.

<sup>b</sup> Derived as follows: [Unit cost of RFA × Proportion of patients receiving RFA (33%) × One RFA treatment per year (1)] + [Unit cost of PEI × Proportion of patients receiving PEI (33%) × Six PEI treatments per year (6)].

<sup>c</sup> Derived as follows: Unit cost of TACE (£537) × Proportion of patients receiving TACE (33%) × One TACE treatment per year (1).

<sup>d</sup> In addition to the medical costs associated with both the underlying level of cirrhosis and untreatable HCC.

**TABLE 42** Selection of parameter estimates: utility for compensated cirrhosis, decompensated cirrhosis and HCC

Six studies reviewed:								
<b>Studies excluded (4):</b>		<ul style="list-style-type: none"> <li>• Two reported expert-derived estimates<sup>437,438</sup></li> <li>• Two used instruments other than EQ-5D<sup>314,439</sup></li> </ul>						
<b>Data extracted from two studies:</b>								
	Study	Country	Instrument	Pop.	N	Utility estimate		
						Comp. cirrhosis	Decomp. cirrhosis	HCC
<b>Study rejected</b>	Thein <i>et al.</i> , 2005 <sup>440</sup>	Canada, Spain <sup>a</sup>	SF-36	HCV	64	0.76 <sup>b</sup>	0.69 <sup>c</sup>	0.67 <sup>d</sup>
<b>Study selected</b>	Chong <i>et al.</i> , 2003 <sup>312</sup>	Canada	EQ-5D	HCV	24	0.75 <sup>c</sup>	0.66 <sup>c</sup>	0.64 <sup>c</sup>
<sup>a</sup> Using combined data from studies by Chong <sup>312</sup> and Cordoba. <sup>313</sup> <sup>b</sup> Derived from SF-36 using the Nichol method. <sup>c</sup> Using UK social preference weights. <sup>441</sup>								

criteria were used to select the quality of life (utility) estimate for each health state. Estimates were preferred if:

- they were based on self-reported quality of life by patients with the relevant health state using validated, standard instruments for utility or quality of life assessment [e.g. EQ-5D, Health Utility Index (HUI) or SF-36]; and
- UK population 'societal preference weights' exist for the full range of health states described (e.g. EQ-5D), or an algorithm exists that enables the derivation of UK population-based preference weights (e.g. SF-6D from SF-36 responses).

Several additional factors were considered in determining the most appropriate utility estimates for use in the models:

- whether a patient's health-related quality of life would be predominantly dependent on the severity of their cirrhosis or the presence and size of any HCC tumours (since most papers classify patients according to their cirrhosis or HCC status, but rarely both)
- whether the method of diagnosis of HCC (i.e. was the tumour discovered because a patient presented symptomatically or as a result of a surveillance programme) might impact on the utility estimate
- whether the clinical situation in which the estimate was obtained (e.g. on the transplant waiting list) might impact on the utility estimate
- whether the constitution of the patient group

(i.e. patients with all types of cirrhosis or only patients with a diagnosis of HCV) might bias the utility estimate.

### Compensated cirrhosis, decompensated cirrhosis and HCC

Six papers were identified reporting the quality of life or utility of patients with compensated cirrhosis, decompensated cirrhosis and HCC (Table 42).

All studies were conducted either in patients with HCV or in patients with cirrhosis of mixed causes. We were unable to identify any studies that provided utility estimates from patients with HBV or alcoholic cirrhosis. However, in two studies<sup>311,439</sup> of patient-based quality of life for different cirrhotic health states, there were no statistically significant differences in utility between respondents with viral versus non-viral cirrhosis in any of the health states assessed. Therefore, utility estimates were applied from studies of patients with HCV-related cirrhosis to patients with cirrhosis due to HBV and alcohol.

Thein and colleagues<sup>440</sup> conducted a systematic review of utility estimates for patients with different stages of chronic HCV in 2004. Within the systematic review, two studies considered patients with compensated and decompensated cirrhosis<sup>312,313</sup> and eight studies considered patients with HCC (although most of these studies were complicated by additional factors such as coinfection with HIV, other co-morbidities and injecting drug use). Chong and colleagues<sup>312</sup>

**TABLE 43** Selection of parameter estimates: mean utility for patients with compensated cirrhosis, decompensated cirrhosis and HCC

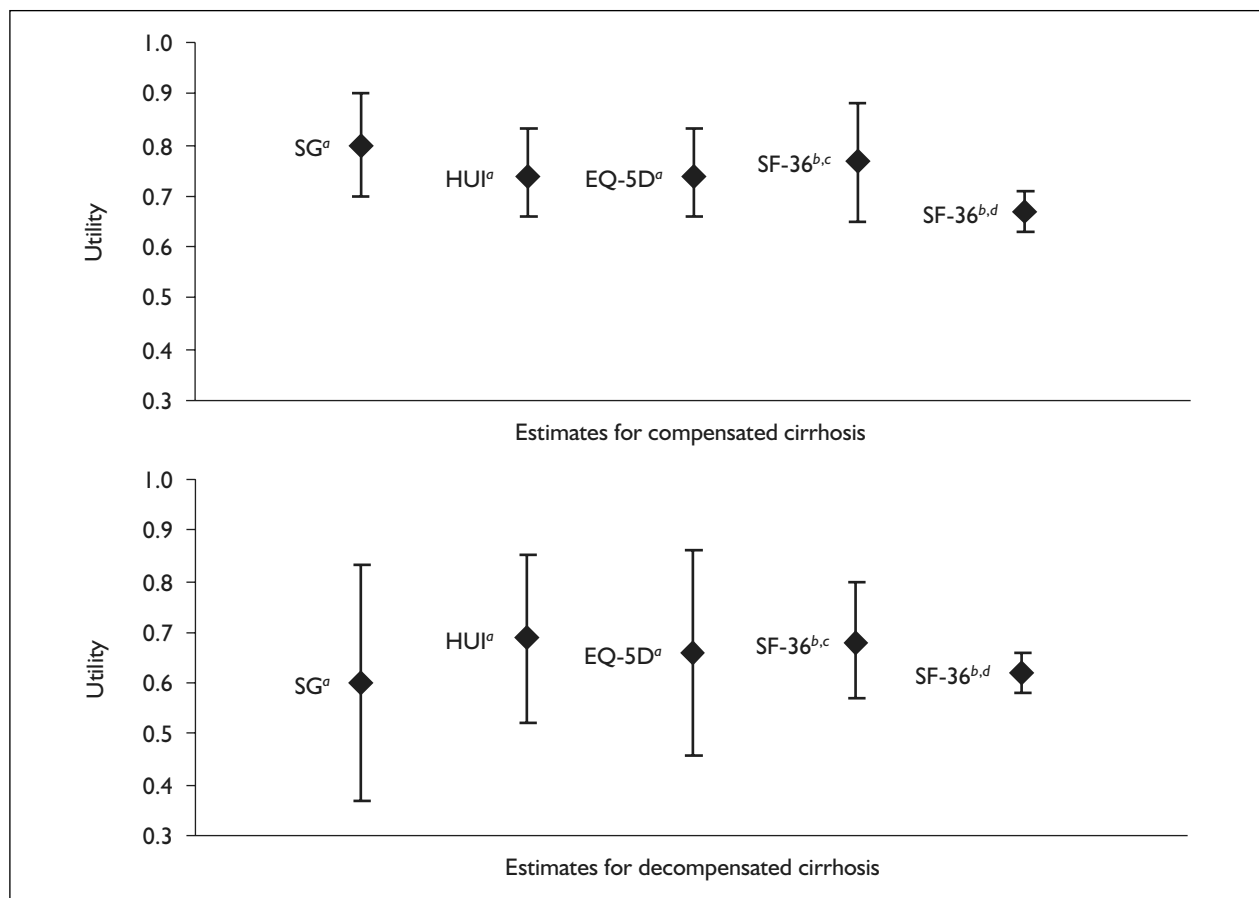
Disease stage	SG <sup>a</sup>	HUI <sup>a</sup>	EQ-5D index <sup>a,b</sup>	SF-36 <sup>c</sup>
Compensated cirrhosis	0.80 (0.70,0.90)	0.74 (0.66,0.83)	0.75 (0.66,0.83)	0.77 (0.65,0.88)
Decompensated cirrhosis	0.60 (0.37,0.83)	0.69 (0.52,0.85)	0.66 (0.46,0.86)	0.68 (0.57,0.80)
HCC	0.72 (0.62,0.82)	0.51 (0.26,0.76)	0.64 (0.44,0.86)	–

Figures in parentheses show the 95% confidence interval.  
<sup>a</sup> Source: Chong et al.<sup>312</sup>  
<sup>b</sup> After the application of UK social preference weights<sup>441</sup> (the published estimates were age-standardised to facilitate comparison across patient groups; to avoid any unnecessary bias, we contacted the authors of the paper who supplied raw EQ-5D response data).  
<sup>c</sup> Source: Cordoba et al.<sup>313</sup> reported in Thein et al.<sup>440</sup> (using the Nichol method for deriving utilities).

measured utilities in Canadian HCV patients with compensated cirrhosis, decompensated cirrhosis and HCC using four methods of utility estimation [visual analogue scales, standard gamble (SG), HUI version 3 and EQ-5D].<sup>312</sup> Cordoba and co-workers<sup>313</sup> measured HRQoL using the SF-36 in patients with compensated and decompensated cirrhosis. Utility weights were derived from the SF-36 data using three different methods. The results from these two papers are shown in Table 43 and Figure 6.

It was assumed that patients with compensated cirrhosis or decompensated cirrhosis, diagnosed with a small or medium HCC tumour, would not experience any decrement in quality of life.

Although it might be reasonable to expect that patients with large (>5 cm) or diffuse tumours would experience reductions in quality of life in addition to those related to cirrhosis, Bianchi and colleagues<sup>315</sup> compared the quality of life (SF-36 and Nottingham Health Profile) of patients with



**FIGURE 6** Utility estimates for compensated and decompensated cirrhosis. Source <sup>a</sup>Chong et al. (2003),<sup>312</sup> <sup>b</sup>Cordoba et al. (2003),<sup>313</sup> reported in Thein et al.<sup>440</sup> Using <sup>c</sup>Nichol method and <sup>d</sup>Fryback method for deriving utilities.



**TABLE 44** Summary of parameter estimates: utility for transplant waiting list, 1 year post-transplant and 2 years post-transplant

	Study	Country	Instrument	N	Population	Utility estimate
Transplant waiting list	Chong <i>et al.</i> , 2003 <sup>312</sup>	Canada	EQ-5D	24	HCV + compensated cirrhosis	0.75
					HCV + decompensated cirrhosis	0.66
1 year post-OLT	Ratcliffe <i>et al.</i> , 2002 <sup>318</sup>	UK	EQ-5D	260	All patients undergoing OLT	0.69 <sup>a</sup>
2 years post-OLT	Ratcliffe <i>et al.</i> , 2002 <sup>318</sup>	UK	EQ-5D	218	All patients undergoing OLT	0.73

<sup>a</sup> 6 months post-OLT used as an estimate of mean utility during the first year post-OLT.

HCC to matched patients with cirrhosis and found few differences. Differences that were observed were not related to tumour size.

However, studies that have measured utility or quality of life in those with HCC have tended to produce utility estimates for people with HCC that are slightly lower than for decompensated cirrhosis (except when using the SG method; see *Table 43*). This utility value for HCC was allocated only to surgically untreatable HCC; in effect (in the Markov model), this means patients with HCC tumours which are large and known.

### Pre- and post-transplantation Transplant waiting list

A summary of the utility estimates used for pre- and post-transplantation states is shown in *Table 44*.

We were unable to identify any data relating to the quality of life of patients listed for transplantation as a result of a diagnosis of HCC. Therefore, quality of life estimates for patients on the transplant waiting list were applied according to the underlying stage of cirrhosis (i.e. utility value for patients with compensated cirrhosis awaiting a transplant 0.75; utility value for patients with decompensated cirrhosis awaiting a transplant 0.66). This is consistent with the findings of several studies in patients with chronic liver disease,<sup>311</sup> with cirrhosis<sup>310</sup> or awaiting liver transplant<sup>316,317</sup> which suggest that, in these patient groups, quality of life is associated with disease (i.e. cirrhosis) severity rather than the underlying cause of liver disease.

These figures are slightly higher than those reported in the UK NHS study of the cost-effectiveness of liver transplantation,<sup>318,435</sup> which reported utility estimates among all patients waiting for a liver transplant of 0.517<sup>435</sup> and

0.53.<sup>318</sup> However, these studies included all patients listed for a liver transplant with no subanalysis of patients with cirrhosis or HCC. These lower estimates are within the range of values used in the sensitivity analyses for decompensated (0.46–0.86) cirrhosis.

We were unable to identify any data to suggest decrements in quality of life directly associated with being listed for a transplant, for example due to additional tests or anxiety associated with waiting for an available organ. Therefore, no 'process utility' decrements were assumed for patients on the waiting list.

### Post-transplantation

Two recently published reports from the UK NHS study into the cost-effectiveness of liver transplantation were identified that include estimates of quality of life following liver transplantation.<sup>318,435</sup> Both studies have large (and overlapping) sample sizes ( $n = 183$  and  $n = 147$ ), but do not provide subanalyses for patients listed for transplantation as a result of an HCC diagnosis. However, the mean utility estimates reported (0.615 and 0.77 at 12 months post-transplantation) are broadly similar to those from a small ( $n = 30$ ) Canadian study of patients with HCV listed for transplantation (mean utility from EuroQol 0.69; from HUI 0.7).

Estimates were taken from the report published by Ratcliffe and colleagues in 2002,<sup>318</sup> which shows that post-transplantation quality of life (as measured by the EQ-5D or SF-36D) seems to increase gradually for approximately 12 months after the transplant and then stabilise. Therefore, the utility estimates at 6 months post-transplantation were used as an estimate of mean utility during the first year post-transplantation. Using regression analysis (random-effects Tobit model) to adjust for other factors, Ratcliffe and

colleagues also showed that post-transplantation EQ-5D utility estimates had no statistically significant association with the type of previous underlying liver disease (patients with cirrhosis versus patients without cirrhosis).

We were unable to find any direct estimates of the quality of life experienced by patients during the month of the transplantation procedure; therefore, a utility value of 0.50 was assumed for this period.

It was assumed that the estimates adopted captured a range of patient experience following liver transplantation; consequently, the parameter was not adjusted to account for probabilities such as tumour recurrence or late graft failure.

#### **Postresection**

We were unable to identify any reliable estimates of utility for patients following liver resection. Poon and colleagues<sup>320</sup> produced quality of life

data from China, using the FACT-G questionnaire, which suggest improvements in quality of life 3 months after the resection procedure, but currently there is no way of deriving utilities from these responses.

In the absence of direct estimates, a utility of 0.50 was assumed for the month in which resection occurs, and it was assumed that following this quality of life reverts to a weighted average of the values (i.e. 0.73) adopted for compensated (0.75) and decompensated cirrhosis (0.66), calculated to approximate the average clinical course. A similar assumption was made by Patel and colleagues<sup>307</sup> in their cost-effectiveness analysis of surveillance for HCC among patients with HCV-related cirrhosis. No account was taken of any diminished quality of life that may accompany HCC recurrence, which is relatively common following resection (see the section 'Treatment for hepatocellular carcinoma', p. 7). This assumption will tend to bias the model in favour of surveillance.

## Chapter 5

### Cost-effectiveness model: results

For each set of outcomes, combined results for the notional mixed aetiology cohort are presented first, followed by a description of separate results for those with ALD-, HBV- and HCV-related cirrhosis. In the results, each of the modelled comparators is referred to using small capital letters (e.g. ANNUAL AFP TRIAGE) to emphasise that these results pertain to the specific operational definition of each screening strategy used in this analysis, rather than a more general interpretation of the screening strategy. Deterministic results (those based on the base-case point-estimate for each input parameter) are presented before the probabilistic results.

#### Effectiveness of surveillance

##### Number needed to be under surveillance

As a measure of the relative effectiveness of the various surveillance strategies, the number of people who need to be under surveillance (NNS) to prevent either a single death from HCC or a single premature death (defined as death prior to the age of 75 years) was calculated (Table 45 and Figure 7).

##### NNS to prevent one death from HCC

Under NO SURVEILLANCE, approximately 20% of the mixed aetiology cohort die as a result of HCC. The effectiveness of the AFP TRIAGE and ULTRASOUND (US) strategies at both annual (14.7%

and 14.9%, respectively) and 6-monthly (12.0% and 12.3%, respectively) intervals is very similar. Increasing the frequency of either AFP TRIAGE or US to 6-monthly has a greater impact on the effectiveness of the surveillance programme than using both tests annually. The most effective surveillance strategy is 6-MONTHLY AFP+US, which reduces the proportion of the cohort dying from HCC to approximately 11%.

The number of people with cirrhosis who need to be under surveillance with either ANNUAL AFP TRIAGE or ANNUAL US in order to prevent one death from HCC is very similar: 19 and 20, respectively. This falls to 11 under combined surveillance with 6-MONTHLY AFP+US.

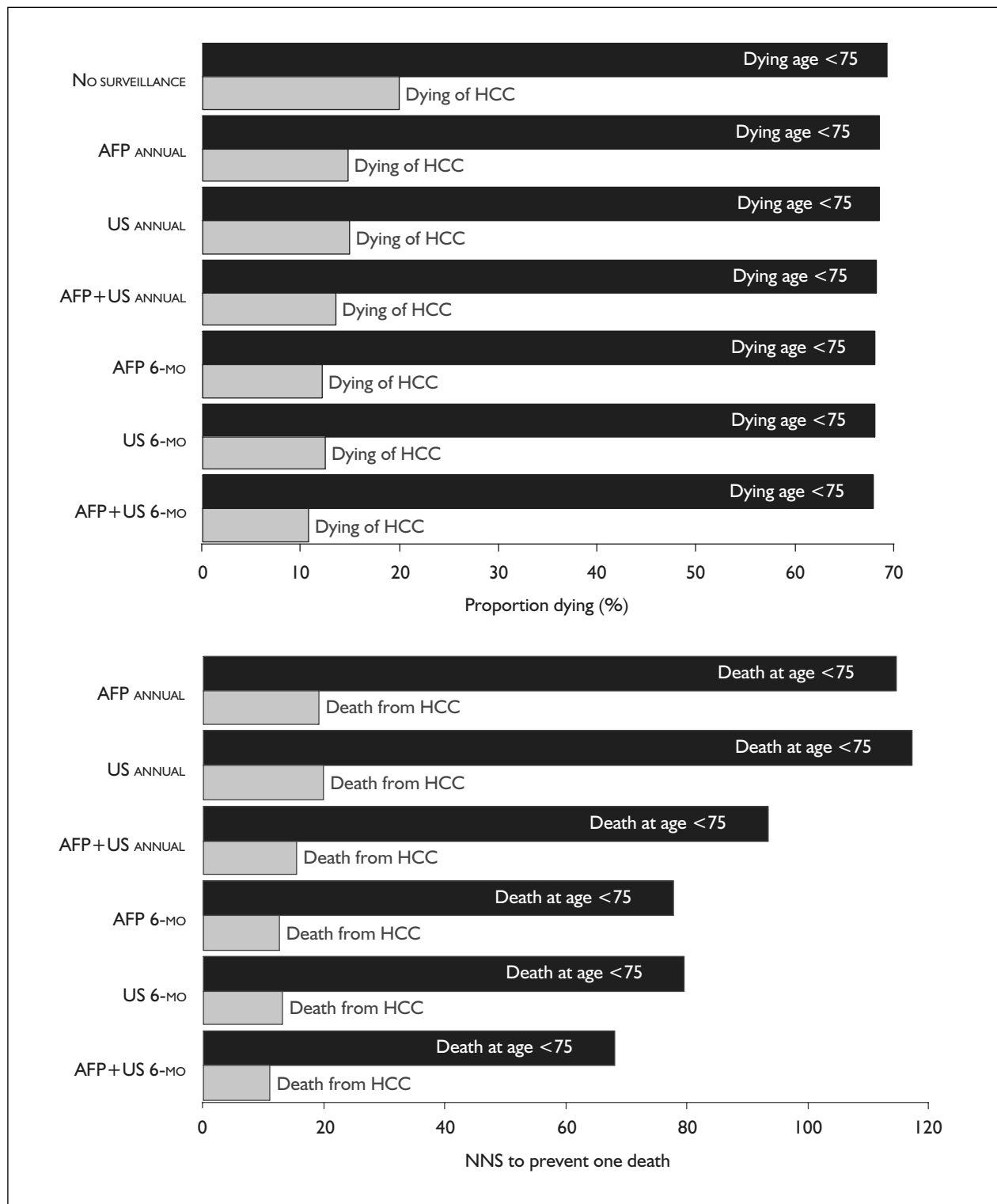
##### NNS to prevent one premature death (before the age of 75)

In the model, when NO SURVEILLANCE is performed, 69.3% of the mixed aetiology population die before they reach the age of 75 years. The impact of regular surveillance for HCC on this proportion is fairly small: the most effective strategy (6-MONTHLY AFP+US) reduces the proportion of people who die by less than two percentage points to 67.8%.

The number of people with cirrhosis who need to be under surveillance with either ANNUAL AFP TRIAGE or ANNUAL US in order to prevent one premature death is very similar: 114 and 117, respectively. This falls to 68 if 6-MONTHLY AFP+US is used.

**TABLE 45** Effectiveness of surveillance: deaths and NNS in mixed aetiology cohort

	No surv.	AFP ANNUAL	US ANNUAL	AFP+US ANNUAL	AFP 6-MO	US 6-MO	AFP+US 6-MO
Proportion dying of HCC	19.9%	14.7%	14.9%	13.5%	12.0%	12.3%	10.8%
NNS to prevent one HCC death		19	20	15	13	13	11
Proportion dead by age 75	69.3%	68.4%	68.5%	68.2%	68.0%	68.0%	67.8%
NNS to prevent one 'premature' death		114	117	93	78	79	68
Mean age of cohort at death	70.08	70.29	70.29	70.34	70.38	70.38	70.43
No surv., no surveillance. Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).							



**FIGURE 7** Effectiveness of surveillance: deaths and NNS in mixed-aetiology cohort. Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).

### Effectiveness of surveillance by cirrhosis aetiology

When the three aetiologies are considered separately, the same pattern of results is observed (Table 46); that is, regular surveillance with AFP

TRIAGE or US is of approximately equal effectiveness at either frequency, and the most effective strategy is 6-MONTHLY AFP+US. Surveillance is most effective for people with HBV-related cirrhosis.

**TABLE 46** Effectiveness of surveillance: deaths and NNS in aetiology-specific cohorts

	No surv.	AFP ANNUAL	US ANNUAL	AFP+US ANNUAL	AFP 6-MO	US 6-MO	AFP+US 6-MO
<b>ALD</b>							
Proportion dying of HCC	17.0%	12.7%	12.9%	11.7%	10.6%	10.8%	9.5%
NNS to prevent one HCC death		23	24	19	16	16	13
Proportion dead by age 75	65.6%	65.0%	65.0%	64.8%	64.7%	64.7%	64.5%
NNS to prevent one premature death		162	166	132	110	112	96
Mean age of cohort at death	71.13	71.27	71.27	71.30	71.33	71.33	71.36
<b>HBV</b>							
Proportion dying of HCC	23.0%	15.9%	16.1%	14.2%	12.4%	12.8%	10.8%
NNS to prevent one HCC death		14	15	11	9	10	8
Proportion dead by age 75	69.8%	67.7%	67.8%	67.3%	66.8%	66.8%	66.4%
NNS to prevent one premature death		48	49	40	33	34	29
Mean age of cohort at death	67.08	67.74	67.73	67.90	68.05	68.04	68.19
<b>HCV</b>							
Proportion dying of HCC	24.1%	17.7%	17.9%	16.1%	14.4%	14.7%	12.8%
NNS to prevent one HCC death		16	16	13	10	11	9
Proportion dead by age 75	75.3%	74.3%	74.3%	74.1%	73.8%	73.8%	73.6%
NNS to prevent one premature death		95	97	78	65	66	56
Mean age of cohort at death	68.98	69.21	69.21	69.26	69.31	69.31	69.36

**NNS to prevent one death from HCC**

In terms of the NNS to prevent one death from HCC, the results from the three separate cohorts are quite similar. Surveillance is slightly more effective in patients with HBV (6-MONTHLY AFP+US reduces the proportion of patients dying as a result of HCC by 52% from 23% to 10.8%; the NNS to prevent one death from HCC using this strategy is 8) than in patients with HCV, and both are more effective than surveillance of patients with ALD (6-MONTHLY AFP+US reduces the proportion of patients dying as a result of HCC by 43% from 17.0% to 9.5%; the corresponding NNS to prevent one death from HCC is 13).

**NNS to prevent one premature death**

The effect of surveillance on the proportion of people dying before the age of 75 is more markedly different between the three aetiologies. Compared with NO SURVEILLANCE, 6-MONTHLY AFP+US increased the number of people living beyond the age of 75 by 11.3% for patients with HBV-related cirrhosis, but only by 6.9% and 3.2% for patients with HCV- and ALD-related cirrhosis, respectively.

**Intermediate model outputs**

These outputs provide an indication of the fate of the individuals in the cohorts, and they are based on event counts at the end of the modelling period, when all members of the cohort are dead. They primarily serve as a reality check of what we

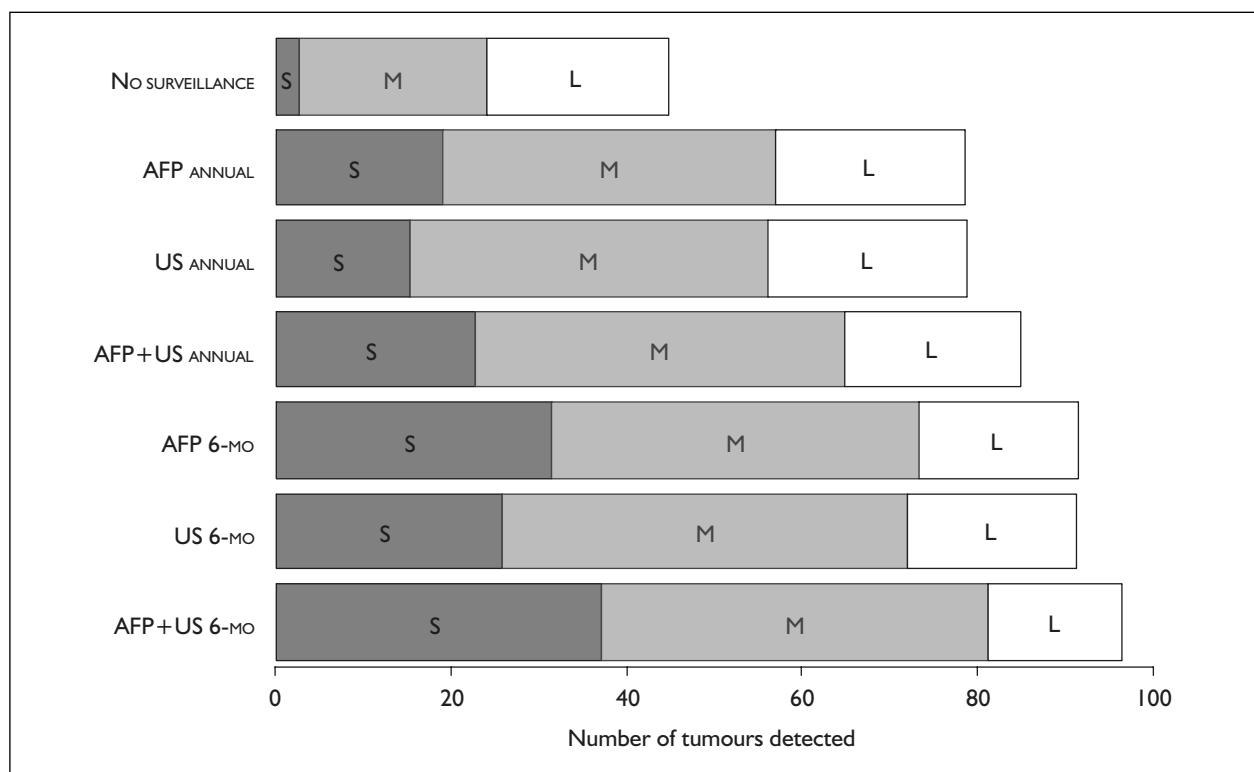
would expect to happen as a result of the introduction of each type of surveillance programme. They could also be considered alongside the cost of each surveillance strategy as a form of cost–consequence analysis.

In each instance, the probabilities have been multiplied by 1000 to give an indication of how many of the events in question would be expected in a cohort of 1000 people.

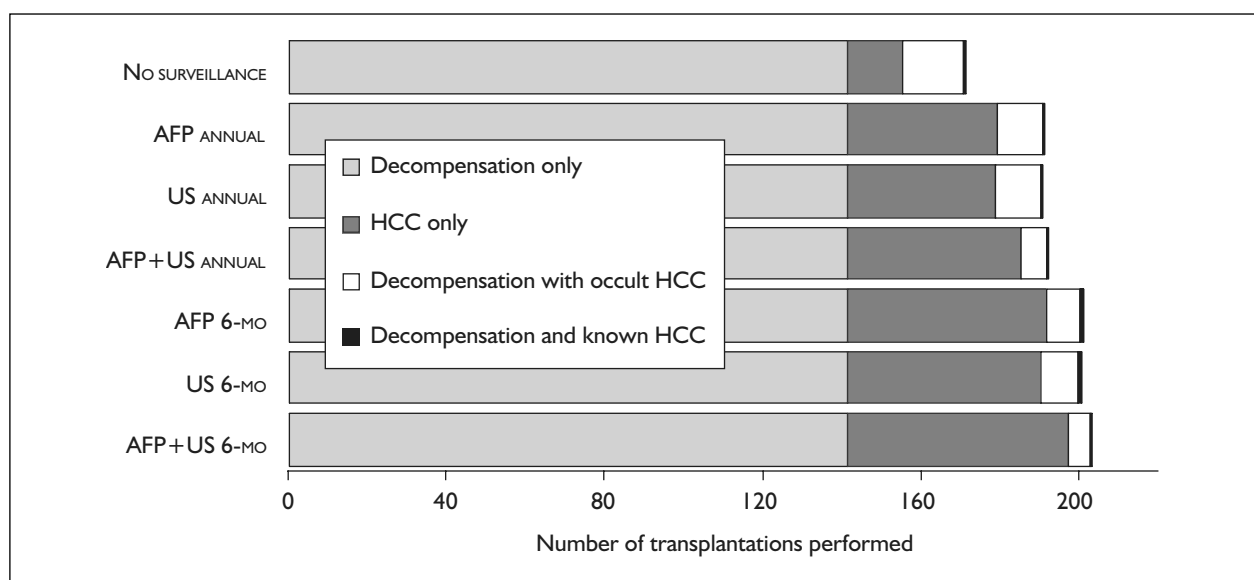
**Tumour size at detection**

Figure 8 illustrates the size of the HCC tumour at detection under each surveillance strategy. All detected tumours are included: those found as a result of symptomatic presentation and surveillance. As might be expected, when no surveillance programme is in operation, there are fewer tumours discovered and most are identified when large in size.

As the intensity of the surveillance programme increases, the total number of tumours identified rises, as does the number of tumours identified while small and medium and potentially amenable to surgical intervention. These results share the main characteristics of the effectiveness outputs. First, increasing the frequency of either AFP TRIAGE or US testing from annual to 6-monthly identifies more tumours at an earlier stage than using both tests annually, and secondly, 6-MONTHLY AFP+US results in the detection of the greatest



**FIGURE 8** Number of HCC tumours and tumour size at detection (in a mixed aetiology cohort of 1000). HCCs detected symptomatically or by screening only (i.e. excluding undetected HCCs). Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV). S, small; M, medium; L, large.



**FIGURE 9** Indications for liver transplantations performed (mixed aetiology cohort of 1000). Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).

number of tumours at a potentially ‘curable’ stage.

**Indications for performed liver transplantations**

Figure 9 illustrates one of the complicating features of the model. All members of the cohort have two

potential indications for OLT: decompensation and detection of an HCC. It shows that, while the model is primarily interested in the treatment of HCC, the majority of people who receive an OLT do so as a result of decompensation rather than detection of a tumour. As would be expected,

surveillance for HCC has no effect on the number of OLTs undertaken for decompensation alone. Therefore, even with a proportion of people with newly diagnosed HCCs receiving hepatic resection (in the base case, 20% of those with small HCCs and 5% of those with medium HCCs), the overall effect of the introduction of any surveillance programme is to increase the number of liver transplants performed. The difference between surveillance strategies is relatively small. However, it appears that the frequency of surveillance is more important than the diagnostic tests adopted (e.g. when compared to ANNUAL AFP TRIAGE, 6-MONTHLY AFP TRIAGE provides a greater increase in transplants than can be achieved with ANNUAL AFP+US).

In the NO SURVEILLANCE strategy, only 8.3% of people receiving OLT have a known tumour, with this proportion rising to 27.9% under 6-MONTHLY AFP+US surveillance.

#### **Number of patients with HCC listed for and receiving liver transplantation**

Figure 10 shows the number of patients with HCC who are listed for OLT, the number who die while on the waiting list, the number who are removed from the waiting list because they are no longer eligible for OLT (e.g. if their tumour grows to a size that contraindicates the procedure) and the number who ultimately receive a transplant.

Similar relationships are observed between surveillance strategies as seen when considering indications for OLT, above.

#### **Number of patients with HCC receiving resection**

Figure 11 shows the number of patients with HCC who have their tumour resected. The absolute number undergoing resection is very small, ranging from 1.6 to 9.5 per 1000 surveilled, according to strategy. This is because, in the base case of the model, the probability of being chosen for resection has been set at a low value. One notable feature of the relationship between strategies is that more patients are assigned to resection under AFP TRIAGE surveillance than under strategies that use US as the primary test. This is because, according to the assumptions of the model, AFP assay is more sensitive at detecting the smallest HCCs than US and small tumours are more likely to receive resection than medium-sized ones. One would expect this relationship to be preserved if the likelihood of resection were raised, so long as the approach remains predominantly used in patients with small tumours.

## **Costs of surveillance**

In the mixed aetiology cohort of cirrhosis patients, the discounted lifetime cost of maintenance in the absence of a surveillance programme is £26,900 per patient (undiscounted cost £38,200 per patient; see Table 48, p. 68). The lifetime cost of the various surveillance strategies ranges from £28,400 per patient for ANNUAL AFP TRIAGE to £30,400 per patient for 6-MONTHLY AFP+US (undiscounted costs £40,300 per patient to £42,900 per patient, respectively).

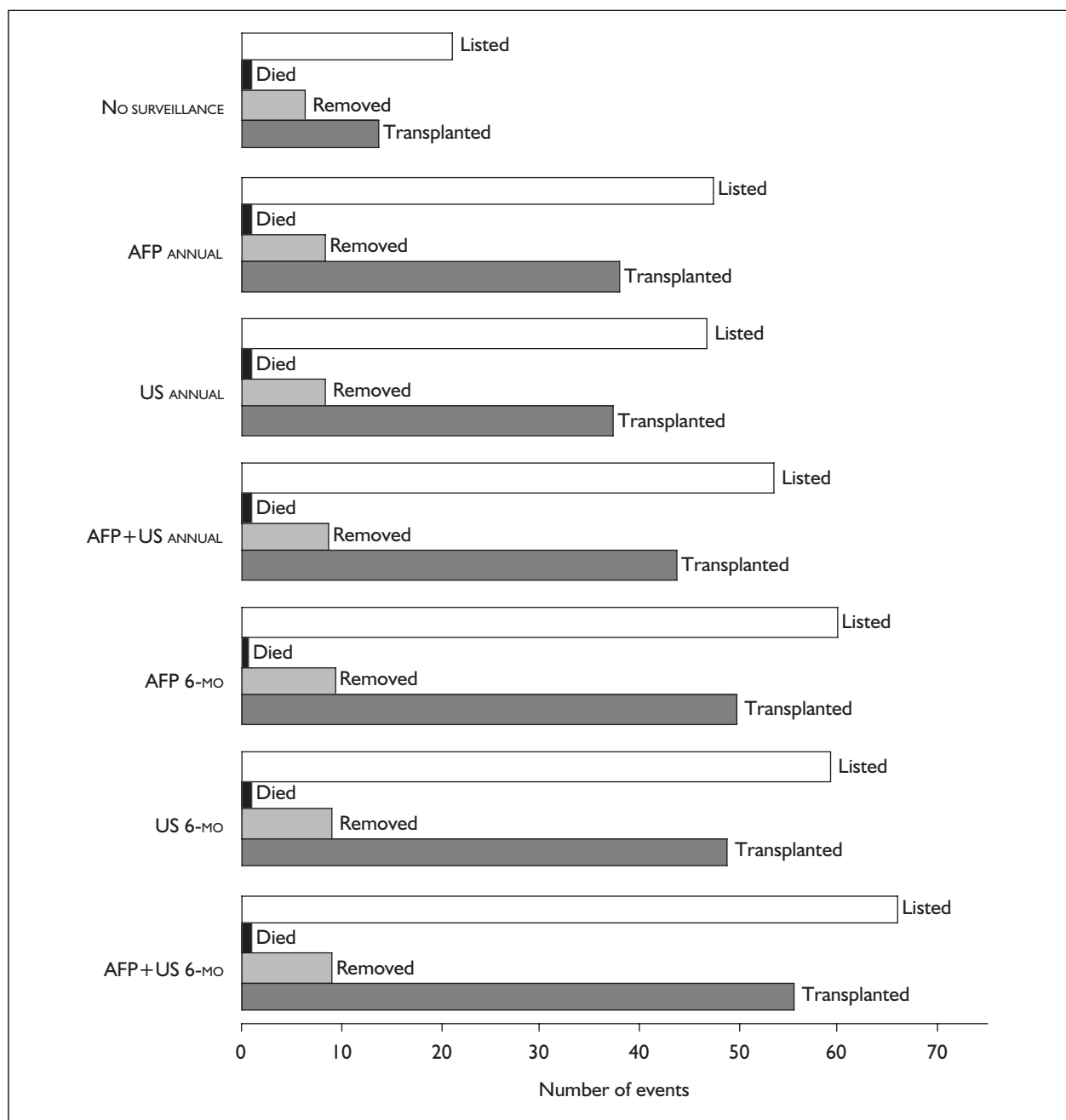
The incremental discounted cost of surveillance compared with NO SURVEILLANCE ranges from £1500 (ANNUAL AFP TRIAGE) to £3500 (6-MONTHLY AFP+US) per person who enters the surveillance programme (Table 50 and Figure 12). Six-monthly surveillance is always more costly than annual surveillance, regardless of the combination of tests used. At either of the surveillance frequencies, regular surveillance with AFP TRIAGE is always the cheapest, and surveillance using AFP+US the most expensive strategy.

Table 47 shows the breakdown of the undiscounted costs (per cohort member), according to whether they relate to surveillance tests, curative treatments (resection and liver transplantation) or the ongoing care costs of being in different disease/health states. It shows that the mean total cost of the surveillance tests are small compared with the routine care costs and curative treatment costs in this patient group. However, screening test costs comprise a much larger proportion of the incremental costs of switching to progressively more intensive surveillance strategies; for example, 7.6% of the £2100 cost of switching from NO SURVEILLANCE to ANNUAL AFP TRIAGE, 25.2% of the £1277 cost of switching from ANNUAL AFP TRIAGE to 6-MONTHLY AFP TRIAGE, and 66% of the £1301 cost of switching from 6-MONTHLY AFP TRIAGE to 6-MONTHLY AFP+US surveillance. Increasing transplant and post-transplant survival costs also comprise a substantial proportion of the incremental costs of switching to progressively more effective surveillance strategies.

## **Cost-effectiveness of surveillance**

### **Cost per additional operable case of HCC identified by surveillance**

For the mixed aetiology cohort, the model estimates that 5% of all patients in the cohort will have an HCC identified at an operable stage in the absence of a surveillance programme. All of



**FIGURE 10** Number of patients with HCC listed for and receiving OLT (mixed aetiology cohort of 1000). Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).

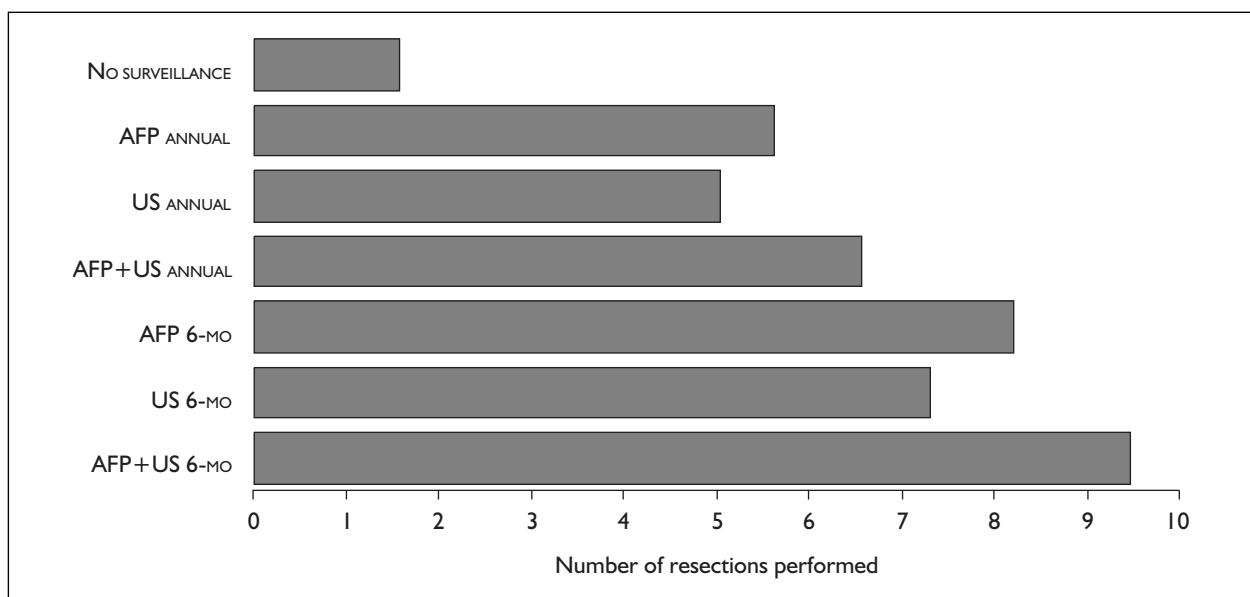
the surveillance programmes result in the identification of more tumours, ranging from approximately 12% with ANNUAL AFP TRIAGE or ANNUAL US to approximately 17% with 6-MONTHLY AFP+US. Regardless of the test or tests used, all of the 6-monthly surveillance strategies result in the identification of more tumours than the annual policies.

Compared with NO SURVEILLANCE, the number of additional operable cases identified ranges from 6.5% with ANNUAL US to 11.8% with 6-MONTHLY

AFP+US. Compared with NO SURVEILLANCE, the most cost-effective surveillance strategy is ANNUAL AFP TRIAGE, with an incremental cost of £22,800 per additional operable case of HCC. The least cost-effective option is 6-MONTHLY AFP+US (£30,000 per additional operable case of HCC).

In the incremental analysis, which examines the cost-effectiveness of progressively more costly interventions, neither of the US strategies would be considered cost-effective, as they are both





**FIGURE 11** Number of patients with HCC receiving resection (mixed aetiology cohort of 1000). Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).

**TABLE 47** Deterministic cost-effectiveness analysis: breakdown of undiscounted costs in mixed aetiology cohort

	No surv.	AFP ANNUAL	US ANNUAL	AFP+US ANNUAL	AFP 6-MO	US 6-MO	AFP+US 6-MO
<b>Tests (£)</b>							
AFP	0	44	0	43	85	0	84
US	0	65	545	543	121	1,061	1,054
CT	0	44	43	82	263	79	155
False-positive costs	0	6	19	23	12	37	45
<b>Total tests (£)</b>	<b>0</b>	<b>159</b>	<b>607</b>	<b>691</b>	<b>481</b>	<b>1,176</b>	<b>1,339</b>
<b>Surgery (£)</b>							
Resection	20	69	62	80	100	89	115
Transplantation	9,153	10,173	10,151	10,414	10,670	10,638	10,903
<b>Total surgery (£)</b>	<b>9,173</b>	<b>10,241</b>	<b>10,212</b>	<b>10,494</b>	<b>10,770</b>	<b>10,727</b>	<b>11,017</b>
<b>Maintenance (£)</b>							
Compensated cirrhosis	15,823	15,565	15,583	15,503	15,421	15,449	15,354
Decompensated cirrhosis	4,856	4,820	4,823	4,811	4,797	4,802	4,786
HCC	47	66	65	70	75	75	80
Postresection	85	309	277	362	456	405	523
Post-transplantation	8,126	9,034	9,014	9,249	9,478	9,448	9,686
Palliative/untreatable	96	111	115	109	104	109	97
<b>Total maintenance (£)</b>	<b>29,032</b>	<b>29,904</b>	<b>29,877</b>	<b>30,105</b>	<b>30,331</b>	<b>30,288</b>	<b>30,526</b>
<b>Total (£)</b>	<b>38,205</b>	<b>40,305</b>	<b>40,697</b>	<b>41,289</b>	<b>41,581</b>	<b>42,192</b>	<b>42,883</b>

Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).

slightly less effective and more costly than surveillance at the same frequency with AFP TRIAGE.

For the mixed aetiology cohort, switching from a NO SURVEILLANCE policy to ANNUAL AFP TRIAGE identifies additional operable cases of HCC at an

estimated cost of £22,800 per HCC identified. Switching from this surveillance policy to the next most effective (and non-dominated) policy of 6-MONTHLY AFP TRIAGE implies an incremental cost of £28,400 per operable HCC identified (Table 48).

**TABLE 48** Deterministic cost-effectiveness analysis: cost per additional operable case of HCC in mixed aetiology cohort

Strategy	Cost (£) <sup>a</sup>	Operable HCCs identified <sup>b</sup>	Compared to NO SURVEILLANCE			Compared to next cheapest cost-effective strategy		
			Incr. cost (£)	Additional operable HCCs	Incr. £/operable HCC	Incr. cost (£)	Additional operable HCCs	Incr. £/operable HCC
NO SURVEILLANCE	26,900	0.051						
AFP ANNUAL	28,400	0.119	1,500	0.068	22,800	1,500	0.068	22,800
US ANNUAL	28,800	0.117	1,900	0.065	28,400	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	29,200	0.135	2,300	0.084	27,500	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	29,400	0.153	2,500	0.102	24,700	1,000	0.034	28,400
US 6-MO	29,900	0.150	3,000	0.098	30,500	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	30,400	0.169	3,500	0.118	30,000	1,000	0.016	64,300

Ext. dom., extendedly dominated; incr., incremental.  
 Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).  
<sup>a</sup> Average cost per patient (discounted at 3.5% per annum).  
<sup>b</sup> Proportion of all patients in the cohort who have an HCC identified at an operable stage; not discounted.

### Cost-effectiveness in people with different cirrhosis aetiology

Cost-effectiveness results for each of three aetiologies are presented in *Table 49*. Unlike the cost–utility results (presented below), surveillance is most likely to be cost-effective on the basis of this outcome in the HCV cohort, although results for all three cohorts are very similar.

The cheapest non-dominated surveillance strategy in all three aetiological subgroups is annual AFP testing, with an incremental cost per additional operable case of HCC identified of £21,900 in the HCV cohort and £23,500 and £24,100 in the ALD and HBV cohorts, respectively. Switching from this surveillance policy to the next most effective (and non-dominated) policy of 6-monthly testing with AFP implies an incremental cost of £25,500 per operable HCC identified in those with HCV-related cirrhosis. Among those with ALD- and HBV-related cirrhosis, the incremental cost-effectiveness of doubling the frequency of surveillance with AFP tests implies a cost per operable HCC case identified of between £30,000 and £31,000.

### Cost per QALY

For the mixed aetiology cohort, the model estimates a total discounted quality-adjusted life expectancy of 9.021 QALYs per patient (undiscounted 12.855 QALYs per patient) in the absence of a surveillance programme (*Table 50*). All of the surveillance strategies produce additional quality-adjusted life expectancy, ranging from a total of 9.096 QALYs per patient

(undiscounted 12.999 QALYs per patient) in a strategy using either ANNUAL AFP TRIAGE OR ANNUAL US to 9.148 QALYs per patient (undiscounted 13.100 QALYs per patient) with 6-MONTHLY AFP+US. All of the 6-monthly surveillance policies produce more QALYs than annual surveillance with any combination of tests.

The incremental discounted QALY gain compared with NO SURVEILLANCE ranges from 0.074 QALYs per patient (equivalent to 27 days in perfect health) for ANNUAL US to 0.126 QALYs per patient (equivalent to 46 days) for 6-MONTHLY AFP+US. For completeness, the effectiveness and cost-effectiveness of each strategy compared directly with no surveillance are shown. However, it is more important to look at the incremental cost-effectiveness implied by moving from cheaper to progressively more costly and effective surveillance strategies.<sup>330</sup>

In the incremental analysis, neither of the ultrasound strategies would be considered (since they are both slightly less effective and more costly than surveillance at the same frequency with AFP TRIAGE). For example, compared with NO SURVEILLANCE, ANNUAL AFP TRIAGE costs an additional £1500 per patient and provides 0.075 QALYs per patient, while ANNUAL US is slightly more costly (£1900 per patient) and provides slightly fewer QALYs (0.074 QALYs per patient). This pattern is evident in both the discounted and undiscounted results. However, it should be noted that joint parameter uncertainty is not taken into account in the deterministic analysis.

**TABLE 49** Deterministic cost-effectiveness analysis: cost per additional operable case of HCC in aetiology-specific cohorts

Strategy	Cost (£) <sup>a</sup>	Operable HCCs identified <sup>b</sup>	Compared to NO SURVEILLANCE			Compared to next cheapest cost-effective strategy		
			Incr. cost (£)	Additional operable HCCs	Incr. £/operable HCC	Incr. cost (£)	Additional operable HCCs	Incr. £/operable HCC
<b>ALD</b>								
NO SURVEILLANCE	26,100	0.044						
AFP ANNUAL	27,400	0.097	1,300	0.054	23,500	1,300	0.054	23,500
US ANNUAL	27,700	0.095	1,600	0.052	31,200	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	28,100	0.110	2,000	0.066	29,900	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	28,200	0.124	2,100	0.081	26,000	800	0.027	31,000
US 6-MO	28,800	0.121	2,600	0.078	34,000	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	29,200	0.137	3,100	0.093	33,300	1,000	0.012	80,200
<b>HBV</b>								
NO SURVEILLANCE	29,600	0.061						
AFP ANNUAL	31,700	0.150	2,100	0.089	24,100	2,100	0.089	24,100
US ANNUAL	32,100	0.147	2,500	0.086	29,200	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	32,700	0.170	3,100	0.109	28,500	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	33,000	0.192	3,400	0.131	26,000	1,300	0.042	30,000
US 6-MO	33,600	0.188	4,000	0.127	31,400	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	34,200	0.212	4,700	0.151	31,100	1,300	0.020	65,000
<b>HCV</b>								
NO SURVEILLANCE	27,600	0.062						
AFP ANNUAL	29,500	0.148	1,900	0.086	21,900	1,900	0.086	21,900
US ANNUAL	29,700	0.145	2,100	0.084	25,500	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	30,300	0.169	2,700	0.107	25,000	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	30,600	0.192	3,000	0.130	23,100	1,100	0.044	25,500
US 6-MO	31,000	0.188	3,400	0.126	26,800	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	31,600	0.213	4,000	0.151	26,500	1,000	0.021	48,300

<sup>a</sup> Average cost per patient (discounted at 3.5% per annum).  
<sup>b</sup> Proportion of all patients in the cohort who have an HCC identified at an operable stage; not discounted.

Therefore, in a mixed aetiology cohort (ALD:HBV:HCV = 57.6:7.3:35.1) the cheapest surveillance strategy is ANNUAL AFP TRIAGE, which confers QALYs at a cost of £20,700 each. Doubling the screening frequency would increase the mean number of QALYs by another 0.035 QALYs and, assuming a WTP threshold of £30,000 per QALY, 6-MONTHLY AFP TRIAGE would also be considered cost-effective at £27,600 per QALY (Figure 12).

### Cost per QALY in people with different cirrhosis aetiology

Full discounted and undiscounted cost-utility results are presented for cohorts of individuals with ALD-related cirrhosis (Table 51 and Figure 13), those with HBV-related cirrhosis (Table 52 and Figure 14) and those with HCV-related cirrhosis (Table 53 and Figure 15). Surveillance in patients with HBV is the most effective and cost-effective, and surveillance in patients with ALD is least cost-effective.

When the three aetiologies are considered separately, a similar pattern of results is observed

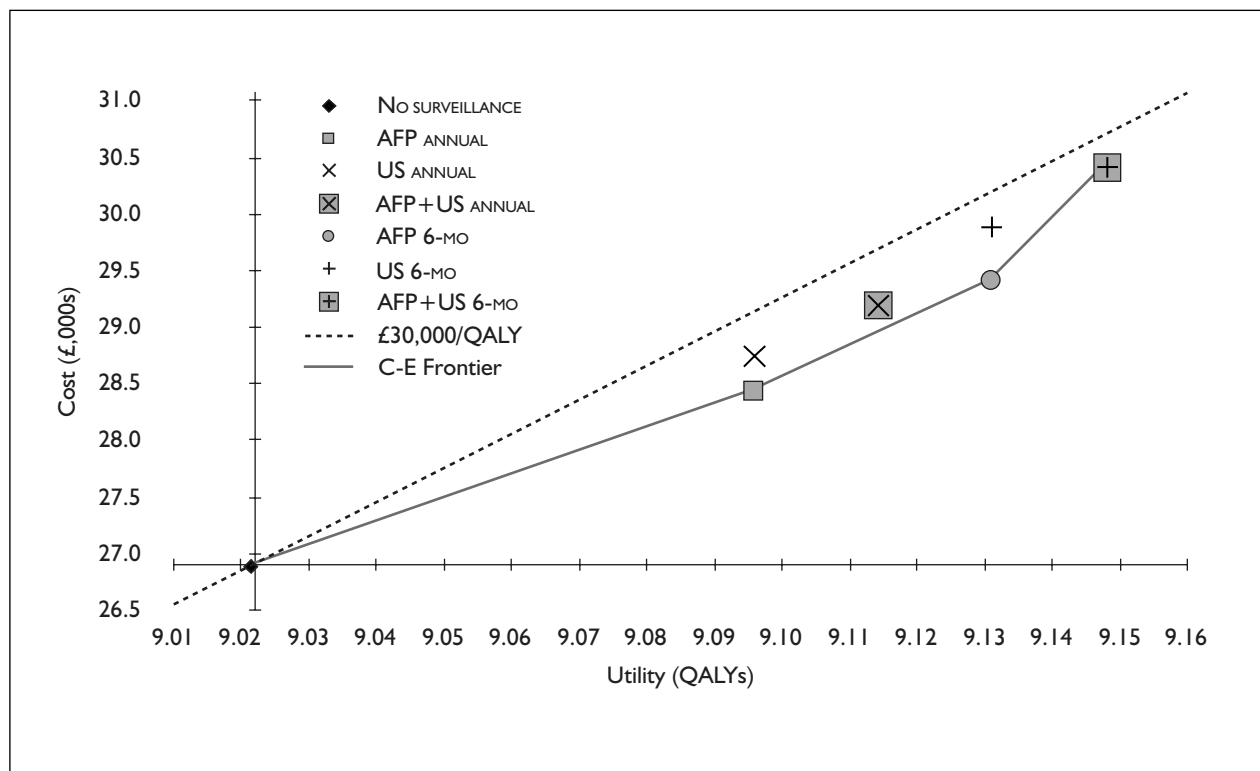
to that shown for the mixed aetiology cohort. In the incremental analyses, compared with the next most costly strategy, ANNUAL AFP TRIAGE is the cheapest non-dominated surveillance strategy, with ICERs of £10,200 per QALY in patients with HBV, £22,200 per QALY in patients with HCV and £24,800 per QALY in patients with ALD.

If only patients with HBV are considered, doubling the surveillance frequency from ANNUAL to 6-MONTHLY AFP TRIAGE gains extra QALYs at a cost of £12,700 per QALY, and 6-MONTHLY AFP+US produces further QALYs at a cost of £26,800 per QALY (discounted results). Overall, if 6-MONTHLY AFP+US were implemented, it would achieve an estimated 0.358 extra QALYs per individual with HBV-related cirrhosis (compared with NO SURVEILLANCE). In contrast, 6-MONTHLY AFP+US for people with ALD-related cirrhosis produces considerably lower QALY gains (0.086 per person) and at a much higher incremental cost. For example, QALYs gained by doubling the frequency of primary AFP assay

**TABLE 50** Baseline results of cost–utility analysis: cost per QALY in mixed aetiology cohort

Strategy	Cost (£)	Utility (QALYs)	Compared to NO SURVEILLANCE			Compared to next cheapest cost-effective strategy		
			Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)	Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)
<b>Discounted</b>								
NO SURVEILLANCE	26,900	9.021						
AFP ANNUAL	28,400	9.096	1,500	0.075	20,700	1,500	0.075	20,700
US ANNUAL	28,800	9.096	1,900	0.074	25,000	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	29,200	9.114	2,300	0.093	24,900	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	29,400	9.131	2,500	0.110	22,900	1,000	0.035	27,600
US 6-MO	29,900	9.131	3,000	0.110	27,400	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	30,400	9.148	3,500	0.126	27,900	1,000	0.017	60,100
<b>Undiscounted</b>								
NO SURVEILLANCE	38,200	12.855						
AFP ANNUAL	40,300	12.998	2,100	0.143	14,700	2,100	0.143	14,700
US ANNUAL	40,700	12.997	2,500	0.142	17,600	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	41,300	13.032	3,100	0.177	17,500	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	41,600	13.065	3,400	0.210	16,200	1,300	0.067	19,000
US 6-MO	42,200	13.064	4,000	0.209	19,100	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	42,900	13.097	4,700	0.242	19,400	1,300	0.032	40,700

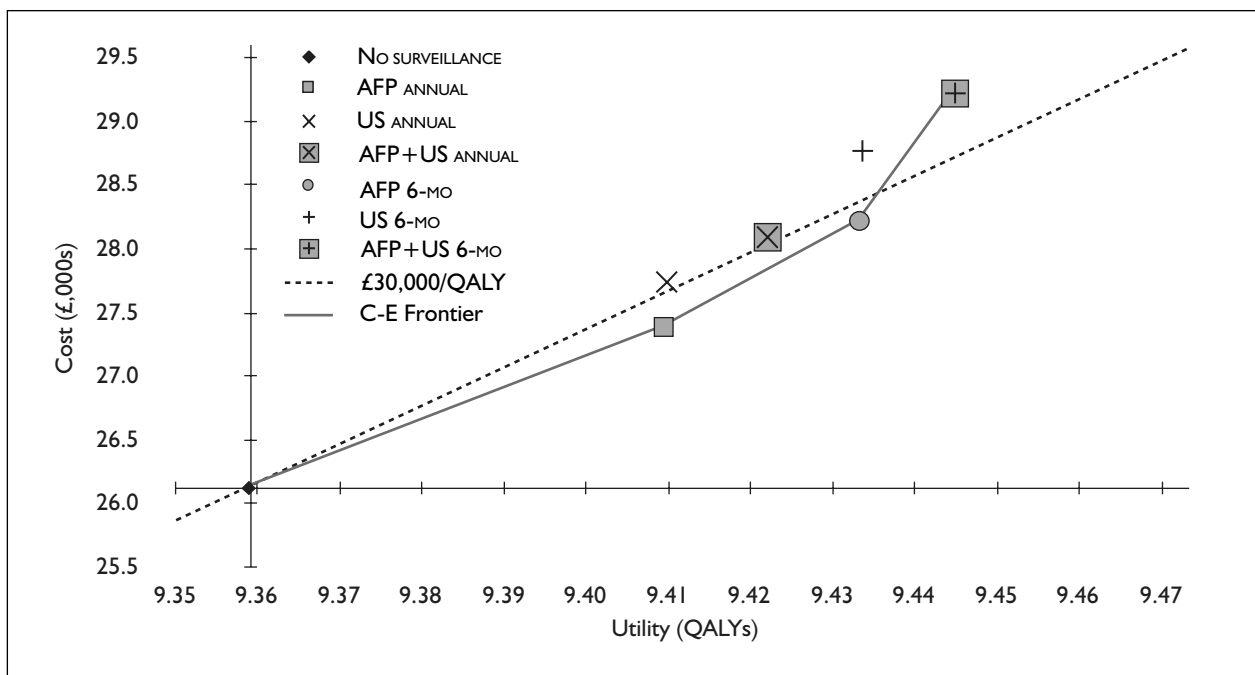
Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).



**FIGURE 12** Baseline results of cost–utility analysis: cost–utility plane showing discounted cost per QALY in mixed aetiology cohort. Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV). C-E, cost-effectiveness.

**TABLE 51** Baseline results of cost–utility analysis: cost per QALY in ALD cohort

Strategy	Cost (£)	Utility (QALYs)	Compared to NO SURVEILLANCE			Compared to next cheapest cost-effective strategy		
			Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)	Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)
<b>Discounted</b>								
NO SURVEILLANCE	26,100	9.359						
AFP ANNUAL	27,400	9.410	1,300	0.051	24,800	1,300	0.051	24,800
US ANNUAL	27,700	9.410	1,600	0.051	31,700	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP+US ANNUAL	28,100	9.422	2,000	0.063	31,400	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	28,200	9.433	2,100	0.074	28,200	800	0.024	35,500
US 6-MO	28,800	9.434	2,600	0.075	35,400	<i>Ext. dom. by AFP 6-MO and AFP+US 6-MO</i>		
AFP+US 6-MO	29,200	9.445	3,100	0.086	36,100	1,000	0.011	88,000
<b>Undiscounted</b>								
NO SURVEILLANCE	37,600	13.429						
AFP ANNUAL	39,300	13.523	1,700	0.094	18,100	1,700	0.094	18,100
US ANNUAL	39,700	13.522	2,100	0.094	22,900	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	40,200	13.545	2,600	0.116	22,600	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	40,400	13.566	2,800	0.138	20,400	1,100	0.044	25,100
US 6-MO	41,100	13.566	3,500	0.137	25,400	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	41,700	13.587	4,100	0.158	25,700	1,300	0.021	61,400



**FIGURE 13** Baseline results of cost–utility analysis: cost–utility plane showing discounted cost per QALY in ALD cohort

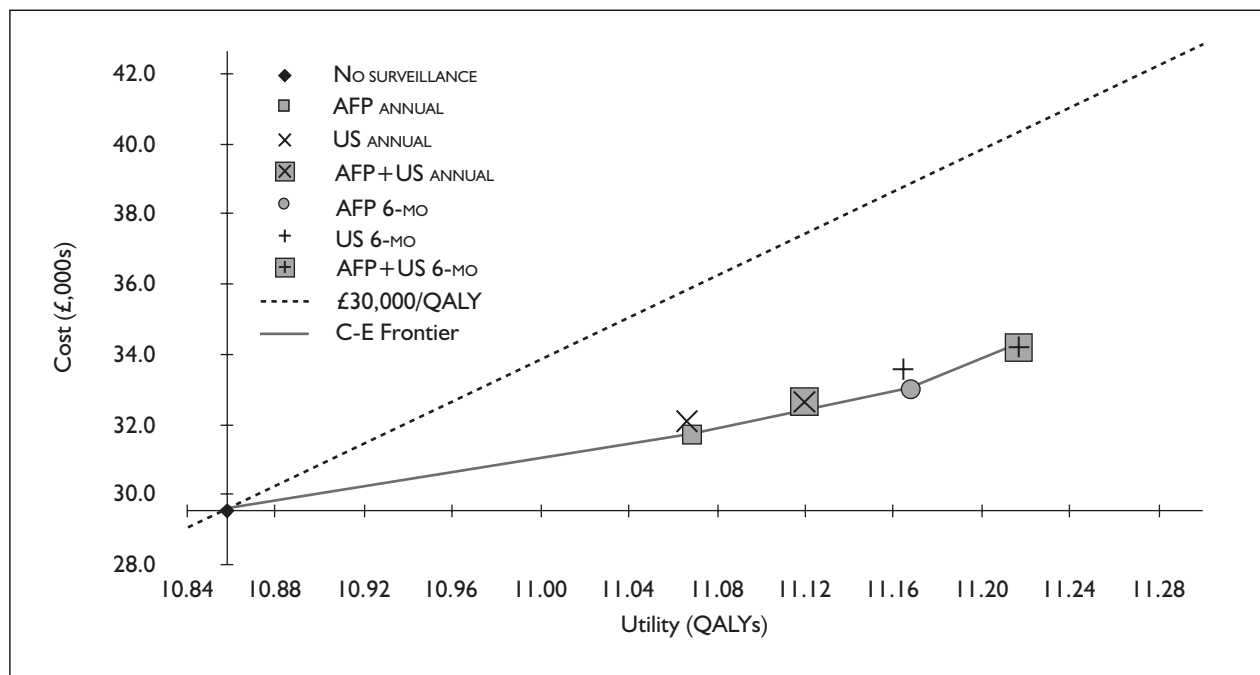
from ANNUAL AFP TRIAGE to 6-MONTHLY AFP TRIAGE cost £35,500 each, and those gained by adding US (to provide 6-MONTHLY AFP+US) cost £88,000 each.

The results for HCV-related cirrhosis show that the cost-effectiveness of surveillance in this group

lies between that for HBV- and ALD-related cirrhosis. At a WTP threshold of £30,000 per QALY, the strategy of 6-MONTHLY AFP TRIAGE would be deemed the most cost-effective, but the extra benefits of adding US for all to this strategy would be achieved at a cost of over £50,000 per QALY.

**TABLE 52** Baseline results of cost–utility analysis: cost per QALY in HBV cohort

Strategy	Cost (£)	Utility (QALYs)	Compared to NO SURVEILLANCE			Compared to next cheapest cost-effective strategy		
			Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)	Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)
<b>Discounted</b>								
NO SURVEILLANCE	29,600	10.858						
AFP ANNUAL	31,700	11.069	2,100	0.211	10,200	2,100	0.211	10,200
US ANNUAL	32,100	11.066	2,500	0.208	12,100	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	32,700	11.119	3,100	0.261	11,900	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	33,000	11.168	3,400	0.310	11,000	1,300	0.099	12,700
US 6-MO	33,600	11.164	4,000	0.306	13,100	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	34,200	11.216	4,700	0.358	13,100	1,300	0.048	26,800
<b>Undiscounted</b>								
NO SURVEILLANCE	45,800	17.073						
AFP ANNUAL	49,200	17.547	3,400	0.474	7,200	3,400	0.474	7,200
US ANNUAL	49,800	17.540	3,900	0.467	8,400	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	50,700	17.659	4,800	0.585	8,300	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	51,200	17.768	5,300	0.695	7,700	1,900	0.221	8,700
US 6-MO	52,000	17.758	6,100	0.684	8,900	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	53,000	17.872	7,200	0.799	8,900	1,800	0.104	17,500



**FIGURE 14** Baseline results of cost–utility analysis: cost–utility plane showing discounted cost per QALY in HBV cohort

## Sensitivity analyses

### One-way sensitivity analyses

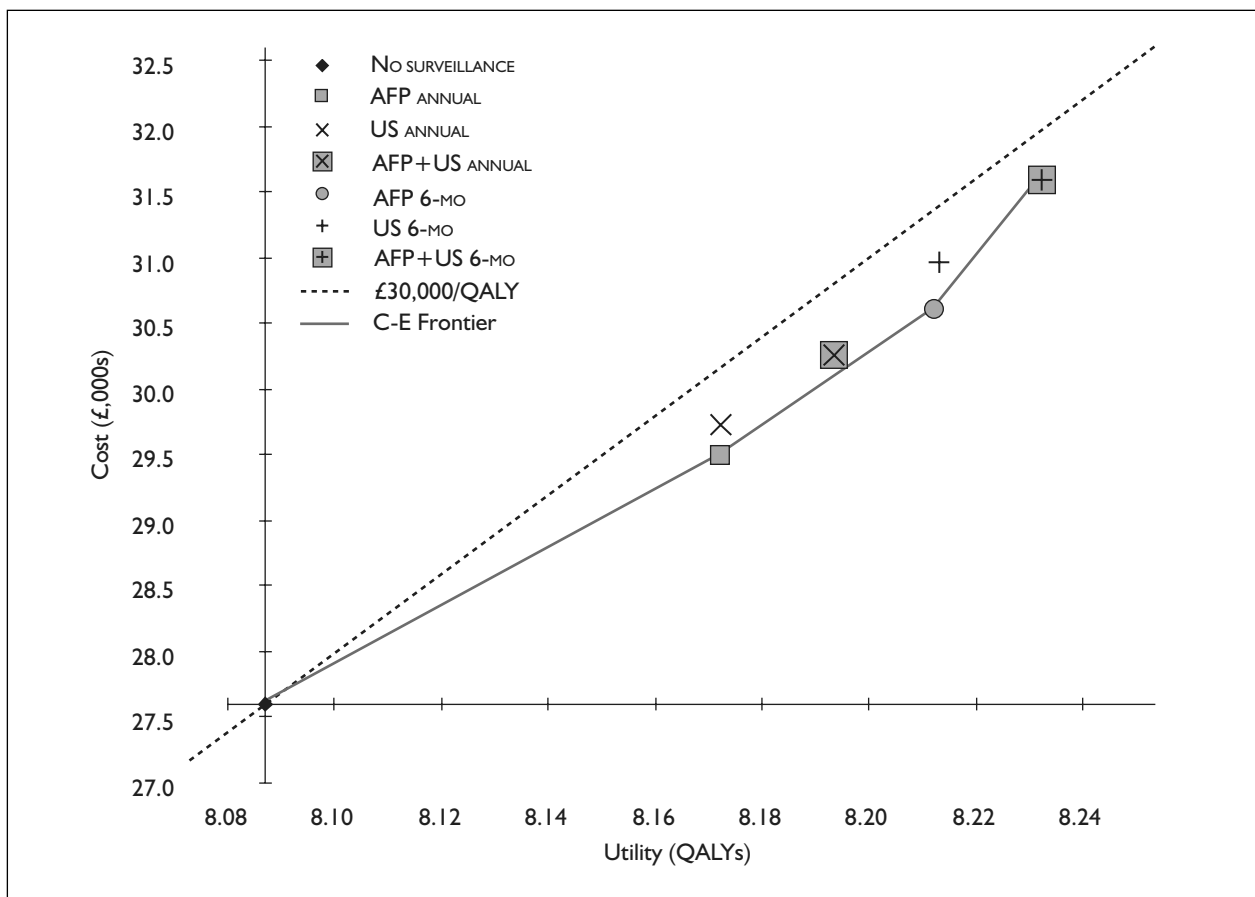
The purpose of the one-way sensitivity analysis is to provide insight into which model inputs have the greatest impact on the cost-effectiveness results, and also to provide an indication of areas

in which further exploration of the uncertainty in the results is warranted.

For simplicity, the analysis was performed in the mixed cohort using the comparison likely to demonstrate these effects most markedly: NO SURVEILLANCE compared with 6-MONTHLY AFP+US.

**TABLE 53** Baseline results of cost–utility analysis: cost per QALY in HCV cohort

Strategy	Cost (£)	Utility (QALYs)	Compared to NO SURVEILLANCE			Compared to next cheapest cost-effective strategy		
			Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)	Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)
<b>Discounted</b>								
NO SURVEILLANCE	27,600	8.087						
AFP ANNUAL	29,500	8.172	1,900	0.085	22,200	1,900	0.085	22,200
US ANNUAL	29,700	8.172	2,100	0.085	25,000	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP+US ANNUAL	30,300	8.193	2,700	0.106	25,100	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	30,600	8.212	3,000	0.126	23,900	1,100	0.040	27,600
US 6-MO	31,000	8.213	3,400	0.126	26,700	<i>Ext. dom. by AFP 6-MO and AFP+US 6-MO</i>		
AFP+US 6-MO	31,600	8.232	4,000	0.145	27,500	1,000	0.020	50,400
<b>Undiscounted</b>								
NO SURVEILLANCE	37,600	11.039						
AFP ANNUAL	40,100	11.195	2,500	0.156	16,100	2,500	0.156	16,000
US ANNUAL	40,400	11.194	2,800	0.155	18,100	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	41,100	11.232	3,500	0.194	18,100	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	41,500	11.269	3,900	0.230	17,000	1,400	0.074	19,300
US 6-MO	42,000	11.268	4,400	0.229	19,200	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	42,800	11.304	5,200	0.265	19,600	1,200	0.035	34,900



**FIGURE 15** Baseline results of cost–utility analysis: cost–utility plane showing discounted cost per QALY in HCV cohort

Figure 16 shows the changes in the ICER of this comparison due to alterations in various input parameters. (The equivalent of Figure 16, but showing variation in net monetary benefit assuming a WTP of £30,000 per QALY for each change in single parameter values, reveals a similar pattern; see Appendix 6.)

The model appears to be most sensitive to changes in transition probabilities, most notably those relating to tumour growth rate, mortality following transplantation and the excess mortality associated with unknown large HCC tumours. Quality of life is also important; in particular, results are sensitive to the utility associated with compensated cirrhosis states and that associated with post-transplantation states. In terms of costs, the costs associated with ultrasound and transplantation appear to be important areas of uncertainty in the model.

Mean age at diagnosis of cirrhosis may be an important variable. Analysis (not shown) suggests that this finding may be particularly exaggerated in patients with HBV (who are likely to be diagnosed at a younger age than individuals with other types of cirrhosis).

Increasing the mortality rate in patients with compensated cirrhosis improves the cost-effectiveness of surveillance.

### Sensitivity to discount rate

Table 54 shows the impact of discount rate on the results of the cost-utility analysis. In the base case, both costs and utilities are discounted at a rate of 3.5%, producing an ICER of £27,900 per QALY for surveillance with AFP and US compared with NO SURVEILLANCE. The results appear to be highly sensitive to the discount rate, with the ICER almost doubling from £19,400 per QALY if no discounting is applied, to £35,800 if equal rates of 6% are applied. This finding is probably to be expected in the setting of a programme that seeks to provide long-term benefit, and that also features an intervention as costly as OLT occurring some way into the future.

### Probabilistic sensitivity analyses

PSA involves using Monte Carlo simulation to explore the impact on cost-effectiveness of the uncertainty in all model parameter values simultaneously. It generates a value for expected costs and expected QALYs for a large number of separately simulated cohorts, with the particular disease and treatment experiences for each cohort (and the resultant costs and effects) being

determined by random selection of parameter values from predefined distributions. These incremental cost and incremental effectiveness pairs can be plotted as a joint distribution on the cost-effectiveness plane. In addition, the values from all simulated individual trials can be aggregated to give the mean expected ICER (which, for any pair of comparators, may be different from the result from the deterministic analysis).

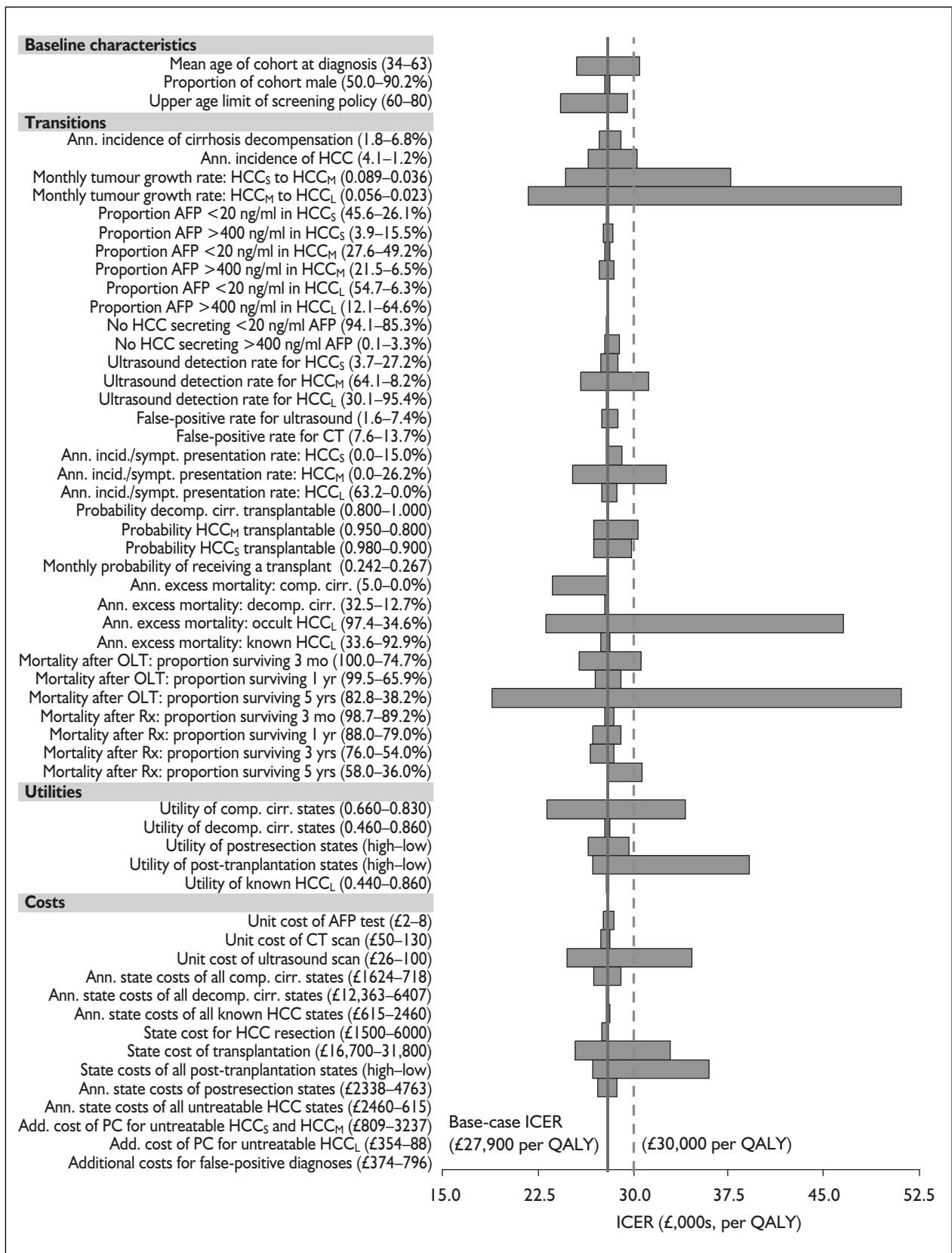
### Comparison of surveillance with AFP and US at 6-monthly intervals with no surveillance

As a simple illustration of the results of the PSA, the analysis was initially performed using the comparison likely to demonstrate the breadth of uncertainty in the model most markedly: NO SURVEILLANCE compared with 6-MONTHLY AFP+US. Figure 17(b) presents the aggregate results of 10,000 simulations per aetiology by using the joint distributions of incremental QALYs and incremental costs to predict the probability that this surveillance strategy is cost-effective when compared with NO SURVEILLANCE, given different WTP thresholds of up to £100,000 per QALY gained [i.e. the cost-effectiveness acceptability curve (CEAC)]. Figure 17(a) shows the joint distribution of the incremental costs and incremental QALYs on the cost-effectiveness plane for a random sample of 1000 simulations per aetiology.

Overall, the results confirm those produced in the deterministic analysis. When compared with NO SURVEILLANCE, 6-MONTHLY AFP+US is most likely to be considered cost-effective (assuming a maximum WTP threshold of £30,000 per QALY) in the HBV cohort and least likely to be considered cost-effective in the ALD cohort. When considering a mixed aetiology cohort, however (i.e. if there is no option of having separate surveillance strategies for people with cirrhosis of different aetiologies), 6-MONTHLY AFP+US can only be concluded as being cost-effective with greater than 50% certainty above a maximum WTP threshold of about £35,000 per QALY. Even with a maximum WTP threshold of £50,000 per QALY there remains a one-in-four chance that surveillance with 6-MONTHLY AFP+US is not cost-effective.

These results, and those for the three aetiologies presented in Appendix 7, should be treated with some caution, however, since they do not account for the costs and utility of less effective and less costly surveillance strategies. In other words, they effectively summarise average cost-effectiveness



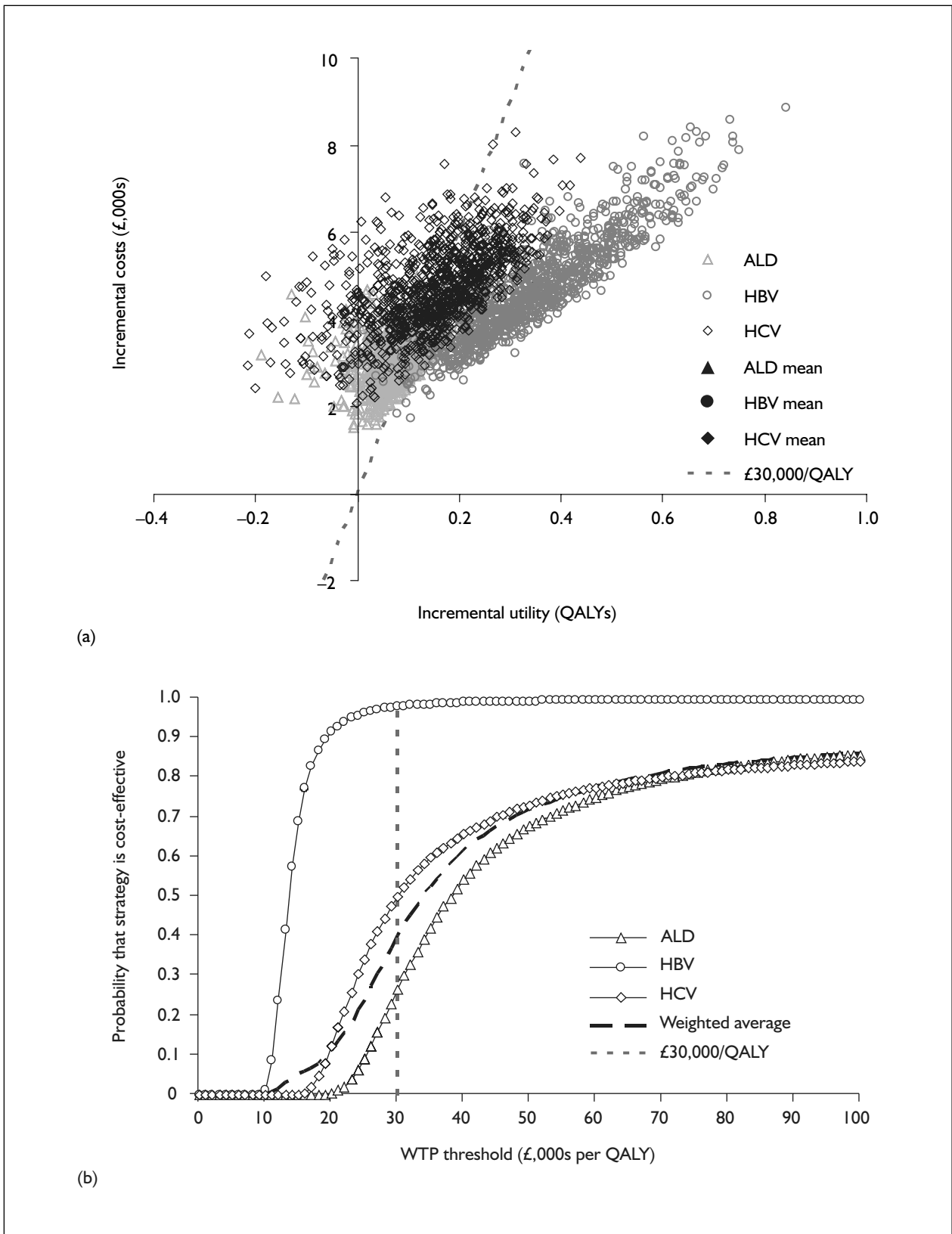


**FIGURE 16** One-way sensitivity analysis (mixed aetiology cohort). Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV). Where different ranges were used for different aetiologies, the range shown gives the minimum and maximum value used in any of the three analyses. add., additional; ann., annual; cirr., cirrhosis; comp., compensated; decomp., decompensated; incid./sympt., incidental/symptomatic; PC, palliative care. Changes in the ICER (6-monthly AFP+US vs no surveillance) due to alterations in parameter values over specified ranges (mixed aetiology cohort).

**TABLE 54** Impact of discount rate on cost-utility of surveillance (mixed aetiology cohort)

Discount rate applied to QALYs	Discount rate applied to costs					
	0.0%	1.5%	3.0%	3.5%	4.5%	6.0%
0.0%	£19,400	£17,000	£15,100		£13,600	£12,300
1.5%	£25,800	<b>£22,700</b>	£20,200		£18,100	£16,400
3.0%	£33,900	£29,800	<b>£26,500</b>		£23,800	£21,500
3.5%				<b>£27,900</b>		
4.5%	£43,900	£38,700	£34,400		<b>£30,900</b>	£27,900
6.0%	£56,300	£49,500	£44,100		£39,600	<b>£35,800</b>

ICERs (6-monthly AFP + US surveillance vs no surveillance) generated with various combinations of discount rates for costs and QALYs. Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).



**FIGURE 17** PSA: incremental cost-effectiveness of 6-MONTHLY AFP+US versus no surveillance. (a) Cost-effectiveness plane, showing incremental cost-effectiveness of 6-monthly surveillance with AFP and US, compared with no surveillance, in a subsample of 1000 Monte Carlo simulations per aetiology. (b) Cost-effectiveness acceptability curve, showing probability that 6-monthly surveillance with AFP and US is cost-effective, compared with no surveillance, at WTP thresholds of up to £100,000 per QALY gained. Weighted average calculated according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV). Based on simulation output for 10,000 trials per aetiology.

ratios that do not reflect the incremental costs and incremental QALYs achieved by changing to the most effective surveillance strategy from less effective (but also less costly) surveillance strategies.

### ALD

In *Figure 17(a)*, the clustering of results from the ALD cohort next to (and crossing) the cost (y) axis shows that, for most simulated trials, this surveillance strategy produces relatively modest QALY gains for the costs invested. *Figure 17(b)* suggests that, assuming a WTP value of £30,000 per QALY, 6-MONTHLY AFP+US would have a one-in-four chance of being considered cost-effective.

### HBV

The horizontal spread of the results from the HBV cohort in *Figure 17(a)* suggests that, in most of the simulated trials, 6-MONTHLY AFP+US produces higher QALY gains for the extra costs invested. It would be highly unlikely, given the specified uncertainty across all parameters in the model, for people with HBV-related cirrhosis to experience a loss in QALYs under this surveillance strategy (compared with NO SURVEILLANCE). *Figure 17(b)* shows that 6-MONTHLY AFP+US would almost certainly be considered cost-effective for values of WTP above £20,000 per QALY.

### HCV

Surveillance of the HCV cohort is likely to have similar cost implications as surveillance of the HBV cohort, but on average will result in the acquisition of fewer than half the number of QALYs. With a WTP threshold of £30,000 per QALY, there is an approximately equal chance that 6-MONTHLY AFP+US would be considered cost-effective or not.

An investigation of the probability that each surveillance strategy is cost-effective compared with NO SURVEILLANCE at various maximum WTP thresholds for the mixed cohort, ALD, HBV and HCV is presented in Appendix 7. Appendix 8 presents these outputs when derived from the pairwise comparisons implied by the deterministic analysis, that is, changing from NO SURVEILLANCE to ANNUAL AFP TRIAGE, changing from ANNUAL AFP TRIAGE to 6-MONTHLY AFP TRIAGE, and changing from 6-MONTHLY AFP TRIAGE to 6-MONTHLY AFP+US.

### Relative probability of maximal cost-effectiveness among the surveillance strategies

*Figures 18–21* show the probability that a given strategy is the most cost-effective in terms of the

highest net monetary benefit (at different levels of WTP for a QALY), averaged across all 10,000 probabilistic simulations, for the mixed cohort, ALD, HBV and HCV, respectively. These graphs are similar to cost-effectiveness acceptability frontiers<sup>442,443</sup> in that they identify the surveillance strategy that is most likely to generate the highest net benefits at each WTP threshold.

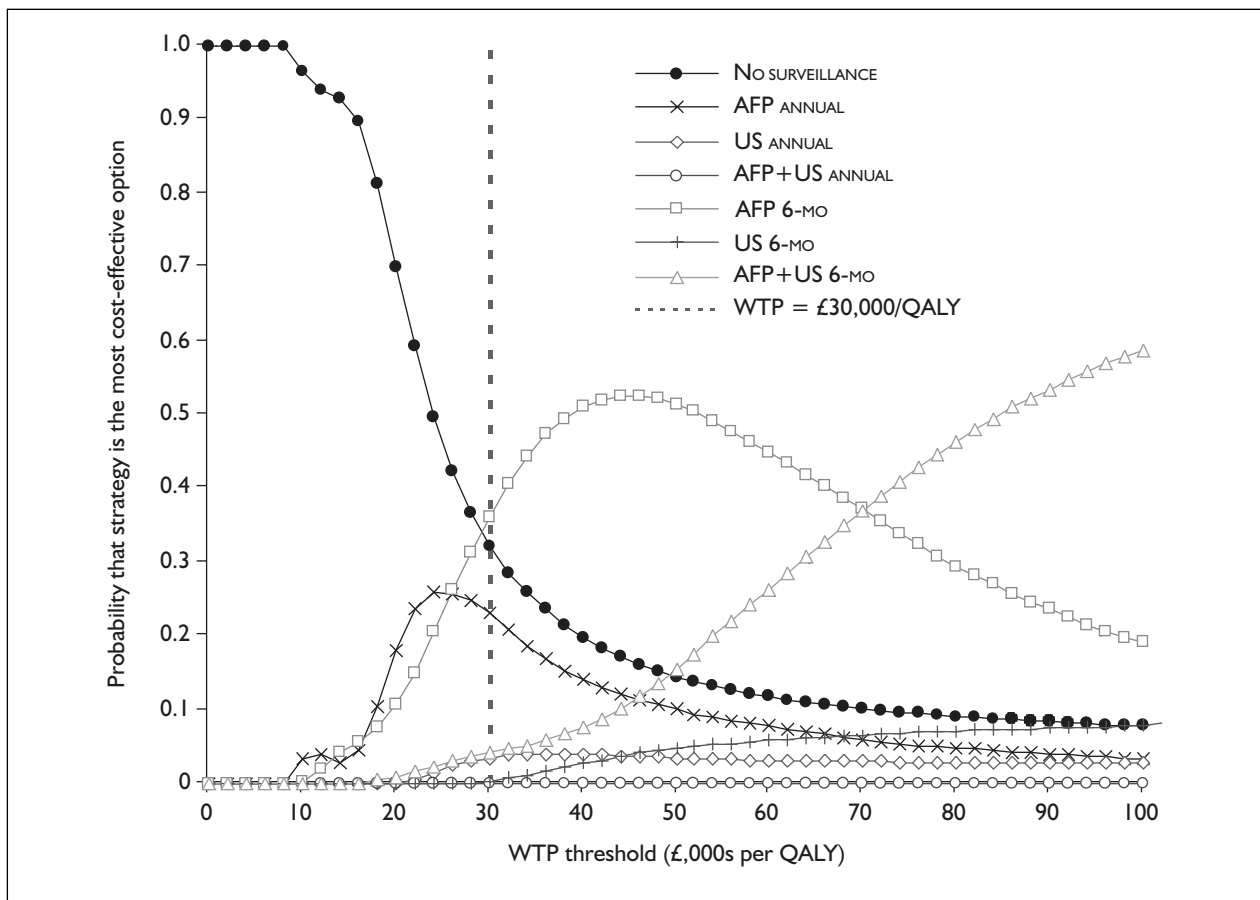
*Figure 18* shows that, at normally accepted thresholds of willingness to pay for a QALY, surveillance using 6-MONTHLY AFP TRIAGE is the most likely strategy to maximise net benefits in the defined mixed aetiology cohort. Below a WTP threshold of about £29,000, NO SURVEILLANCE is likely to generate the highest net benefit. Although the strategy of 6-MONTHLY AFP TRIAGE has the best chance of being cost-effective at and above £30,000 per QALY, the joint uncertainty in the model's parameters is such that only above £38,000 per QALY is there a greater than 50% chance that this strategy generates the highest net benefits. The likelihood that 6-MONTHLY AFP+US is the optimal strategy is only realistic when the WTP per QALY exceeds £80,000.

### ALD

*Figure 19* shows that for WTP levels of £30,000 per QALY or less, NO SURVEILLANCE is most likely to generate the highest net monetary benefit. However, at the upper end of this range (WTP = £28,000–30,000 per QALY), ANNUAL AFP TRIAGE is almost as likely to be the most cost-effective option as NO SURVEILLANCE. Above this WTP level, if incremental cost-effectiveness ratios from £31,000 to £82,000 were to be deemed acceptable, 6-MONTHLY AFP TRIAGE would be the strategy most likely to be considered cost-effective. Nevertheless, the combined parameter uncertainty in the ALD model is such that none of the surveillance strategies can be concluded as being the most cost-effective with more than 60% certainty (until WTP levels exceed £100,000 per QALY).

### HBV

For those with HBV-related cirrhosis (*Figure 20*), a number of surveillance strategies would be cost-effective at different WTP thresholds. From approximately £10,000 to £13,000 per QALY, ANNUAL AFP+US would be the most likely to maximise net monetary benefit. From about £13,000 to about £28,000 per QALY, 6-MONTHLY AFP TRIAGE would be most likely to be considered cost-effective. Above £28,000 per QALY, 6-MONTHLY AFP+US becomes the strategy most likely to yield the highest net monetary benefit.



**FIGURE 18** PSA: relative probability of maximal cost-effectiveness amongst surveillance strategies (mixed aetiology cohort). Probability of each strategy being the most cost-effective, measured in terms of highest net monetary benefit, at WTP thresholds of up to £100,000 per QALY gained. Results are derived from simulation output for 10,000 trials per aetiology, weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).

### HCV

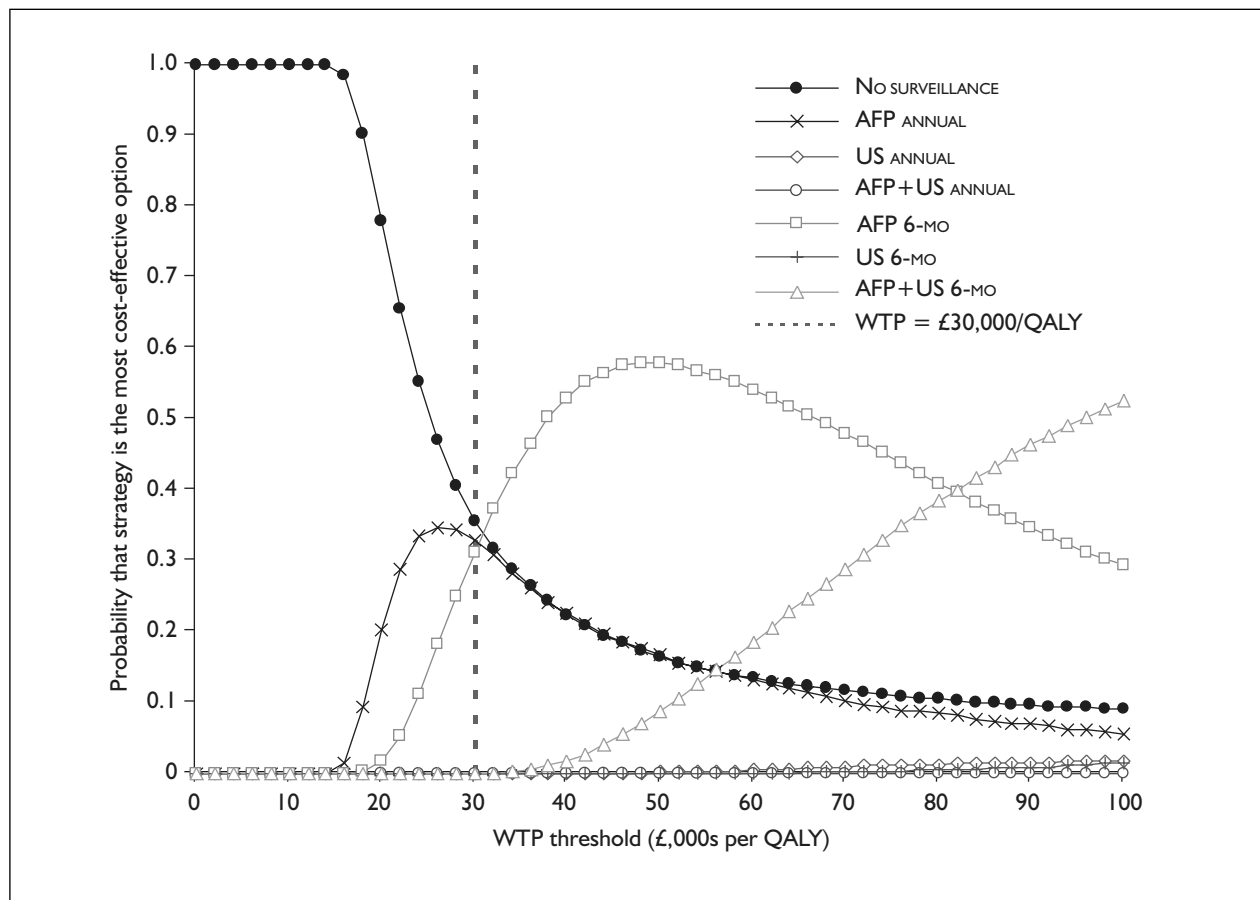
For those with HCV-related cirrhosis (Figure 21), the first surveillance strategy to become more cost-effective (i.e. yield more net monetary benefits on average, across all probabilistic simulations) than NO SURVEILLANCE is 6-MONTHLY AFP TRIAGE, for WTP values of between £27,000 and £64,000 per QALY. Above £64,000 per QALY, 6-MONTHLY AFP+US becomes the strategy most likely to yield the most net monetary benefit. In this cohort alone, there is a small probability that ultrasound-led surveillance strategies generate the most net benefit. This may be related to the higher incidence of HCC in this population, which would entail fewer 'wasted' scans (i.e. true-negative screening events).

In summary, these results show that, using a decision-making approach that relies on thresholds of maximum WTP for a QALY, different surveillance strategies are likely to be

considered the most cost-effective in people with different cirrhosis aetiologies. Table 55 illustrates, for hypothetical maximum WTP values of £20,000, £30,000 and £50,000 per QALY, the optimum surveillance strategies identified by this analysis, taking into account the uncertainty in the model's parameters.

### EVPI analyses

Per-patient global EVPI estimates in aetiology-specific cohorts (assuming a WTP threshold of £30,000 per QALY) are presented in Appendix 9. These confirm that the cost-effectiveness of surveillance in the cohort with HBV-related cirrhosis is much less susceptible to parameter uncertainty. In particular, when each surveillance strategy is compared to the option of NO SURVEILLANCE, no EVPI value exceeds £27 (this is the estimated per-patient cost of establishing the superior cost-effectiveness of 6-MONTHLY AFP+US versus NO SURVEILLANCE).



**FIGURE 19** PSA: relative probability of maximal cost-effectiveness among surveillance strategies (ALD cohort). Probability of each strategy being the most cost-effective, measured in terms of highest net monetary benefit, at WTP thresholds of up to £100,000 per QALY gained. Results are derived from simulation output for 10,000 trials.

In contrast, the identification of optimal decisions is associated with substantial uncertainty, which might be costly to resolve, in the ALD and HCV cohorts.

Population EVPI was not calculated, in the absence of any plausible data on the size of the populations in which these policies might be adopted (i.e. the prevalence of diagnosed ALD-, HBV- and HCV-related compensated cirrhosis in England and Wales).

**Scenario analyses**

The following sections present the cost-utility results relating to several scenarios, which have been chosen

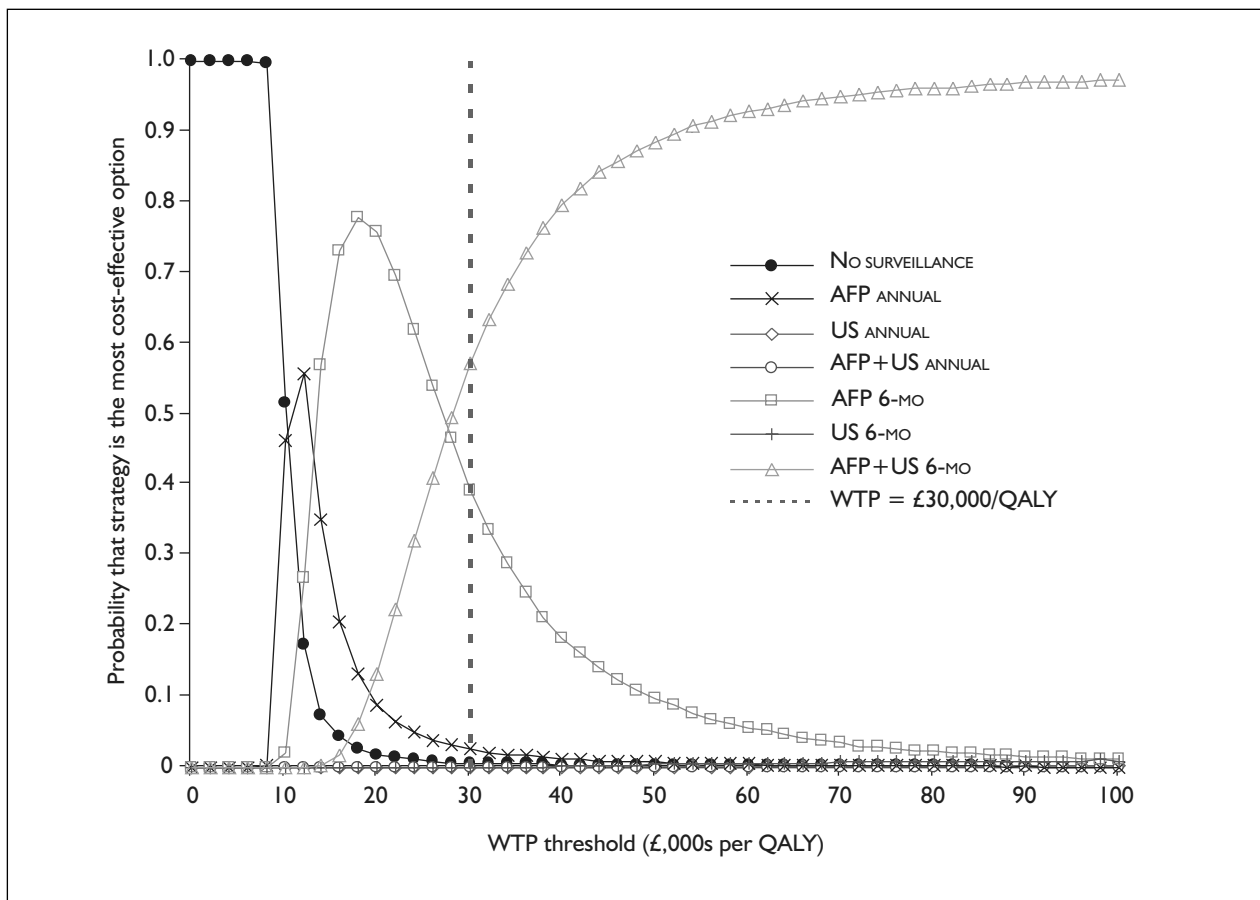
- because they directly reflect gold-standard practice (e.g. liver transplantation only)
- to explore the implications of emerging technologies (e.g. contrast-enhanced ultrasound)
- to reflect the reality of patient behaviour (e.g.

imperfect compliance with recommended surveillance intervals)

- to explore the impact of key simplifying modelling assumptions (such as the reliance on a single average tumour growth rate)
- to explore the impact of longer waiting times for liver transplantation.

**Compliance**

The base case assumes 100% compliance with the surveillance programme (that is, every individual attends every screening appointment). We made this decision because we were keen to observe the characteristics of the surveillance strategies themselves, and felt that non-compliance would introduce extraneous noise to the background from which we were attempting to detect a signal. In recognition of the fact that a perfectly compliant cohort is an extremely unlikely finding in practice, the impact of missed appointments was explored in the following scenario analyses.



**FIGURE 20** PSA: relative probability of maximal cost-effectiveness among surveillance strategies (HBV cohort). Probability of each strategy being the most cost-effective, measured in terms of highest net monetary benefit, at WTP thresholds of up to £100,000 per QALY gained. Results are derived from simulation output for 10,000 trials.

The model recognises two kinds of non-compliance: there is a probability that any screening appointment will be missed, and there is an annual rate at which members of the surveillance cohort drop out of the programme entirely (this does not preclude them from subsequently developing symptomatic disease and requiring treatment). In these analyses, these two parameters were varied simultaneously. *Table 56* shows cost-utility results for a scenario in which 50% of appointments are missed and members of the cohort drop out at a rate of 5% per annum.

*Table 57* shows cost-utility results for a scenario in which 75% of appointments are missed and members of the cohort drop out at a rate of 10% per annum.

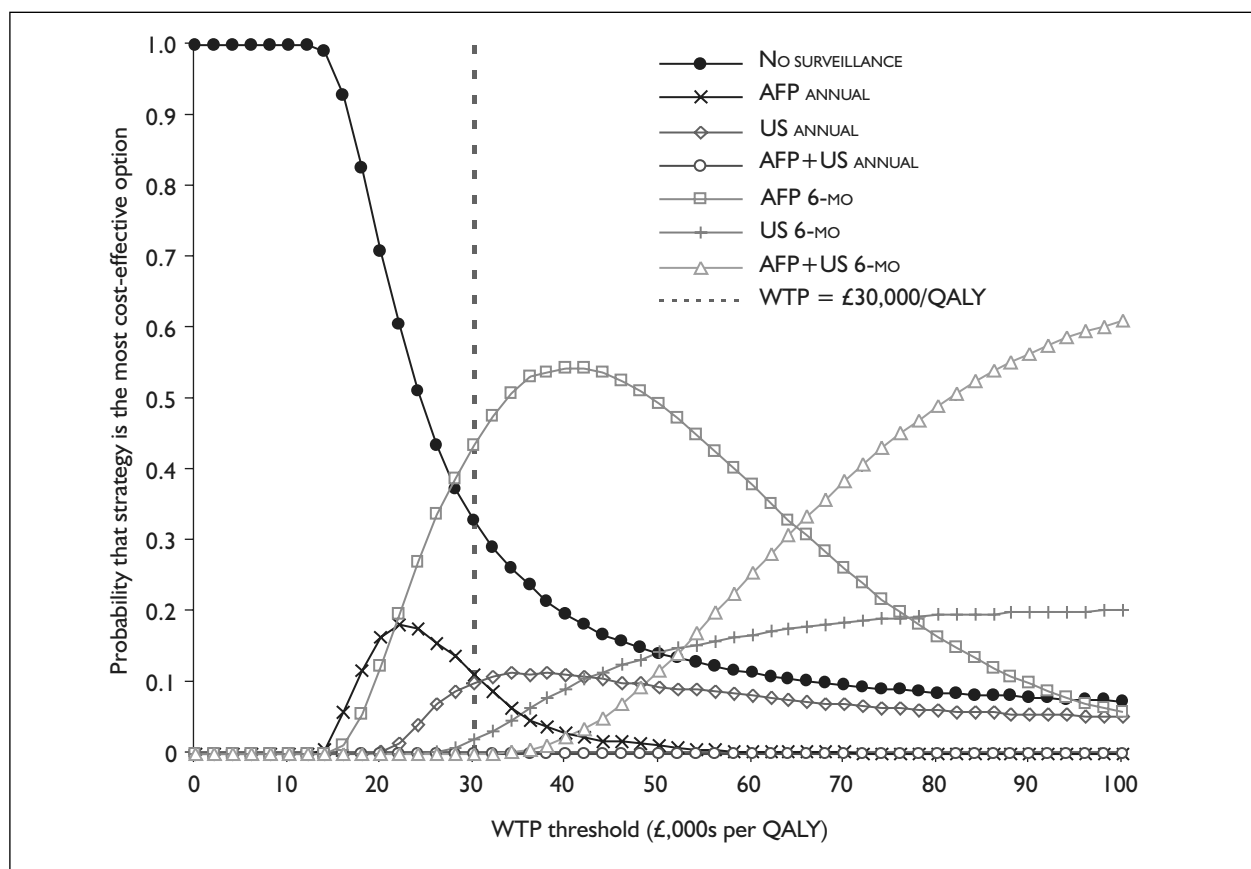
The results suggest that, under conditions of poor compliance, the cost-effectiveness of surveillance is improved. However, this has to be

considered in the light of the very noticeable reduction in effectiveness. Examination of the outputs in terms of net monetary benefit (not shown), which takes into account the relative contributions of changes in benefits (QALYs) and costs, assuming a WTP of £30,000 per QALY, demonstrates that the loss of QALYs with decreasing compliance outweighs the gain in cost-effectiveness.

#### **Stratified tumour growth rates**

One-way sensitivity analysis suggested that the model is very sensitive to transition probabilities governing HCC progression. When tumour growth rates were slowed, cost-effectiveness fell appreciably; conversely, when the parameters were varied to suggest faster progression, surveillance appeared more cost-effective.

In reality, individual tumours do not grow at one homogeneous, average rate. Accordingly, this



**FIGURE 21** PSA: relative probability of maximal cost-effectiveness among surveillance strategies (HCV cohort). Probability of each strategy being the most cost-effective, measured in terms of highest net monetary benefit, at WTP thresholds of up to £100,000 per QALY gained. Results are derived from simulation output for 10,000 trials.

**TABLE 55** Optimal decisions based on best chance of maximising net benefit while reflecting all parameter uncertainty

	WTP threshold (£ per QALY)		
	Approx. £20,000	Approx. £30,000	Approx. £50,000
<b>If a separate surveillance strategy for each aetiology is feasible</b>			
ALD	NO SURVEILLANCE	NO SURVEILLANCE	6-MONTHLY AFP TRIAGE
HBV	6-MONTHLY AFP TRIAGE	6-MONTHLY AFP+US	6-MONTHLY AFP+US
HCV	NO SURVEILLANCE	6-MONTHLY AFP TRIAGE	6-MONTHLY AFP TRIAGE
<b>With one surveillance strategy for all three aetiologies</b>			
Mixed aetiology cohort	NO SURVEILLANCE	6-MONTHLY AFP TRIAGE	6-MONTHLY AFP TRIAGE
Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).			

scenario analysis was constructed to investigate the extent to which the cost-utility of surveillance is influenced by variability in the growth rate of HCCs (that is, the impact of the exact mixture of slow-growing and fast-growing tumours).

For each aetiology of cirrhosis, nine separate analyses were performed, with both of the tumour growth rates that are specified in the model

(HCC<sub>S</sub> to HCC<sub>M</sub> and HCC<sub>M</sub> to HCC<sub>L</sub>) varied simultaneously over nine equal strata, corresponding to tumour volume doubling times from 80 to 203 days (the 95% confidence interval reported in the selected parameter source for tumour growth rate;<sup>324</sup> see above). The results of these analyses were then pooled, with a weighted average cost, utility and cost-utility calculated according to three separate distributions: a normal



**TABLE 56** Scenario analyses: cost-utility with imperfect compliance (50% of appointments missed; 5% per annum of surveillance cohort drop out entirely)

Strategy	Cost (£)	Utility (QALYs)	Compared to NO SURVEILLANCE			Compared to next cheapest cost-effective strategy		
			Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)	Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)
<b>Mixed</b>								
NO SURVEILLANCE	26,900	9.021						
AFP ANNUAL	27,600	9.057	700	0.036	20,500	700	0.036	20,500
US ANNUAL	27,800	9.057	900	0.036	24,300	<i>Dominated by AFP ANNUAL</i>		
AFP 6-MO	28,000	9.069	1,100	0.047	23,700	400	0.011	33,200
AFP+US ANNUAL	28,000	9.068	1,100	0.047	23,800	<i>Dominated by AFP 6-MO</i>		
US 6-MO	28,100	9.071	1,300	0.049	25,500	<i>Ext. dom. by AFP 6-MO and AFP+US 6-MO</i>		
AFP+US 6-MO	28,500	9.083	1,600	0.061	25,400	500	0.014	31,600
<b>ALD</b>								
NO SURVEILLANCE	26,100	9.359						
AFP ANNUAL	26,700	9.383	600	0.025	24,300	600	0.025	24,300
US ANNUAL	26,900	9.383	700	0.024	30,400	<i>Dominated by AFP ANNUAL</i>		
AFP 6-MO	27,000	9.393	900	0.034	26,600	300	0.009	32,600
AFP+US ANNUAL	27,100	9.391	900	0.032	29,700	<i>Dominated by AFP 6-MO</i>		
US 6-MO	27,200	9.392	1,100	0.034	32,400	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	27,500	9.400	1,300	0.042	32,100	400	0.008	55,300
<b>HBV</b>								
NO SURVEILLANCE	29,600	10.858						
AFP ANNUAL	30,500	10.956	1,000	0.098	10,000	1,000	0.098	10,000
US ANNUAL	30,700	10.954	1,100	0.096	11,800	<i>Dominated by AFP ANNUAL</i>		
AFP 6-MO	30,900	10.991	1,400	0.132	10,400	400	0.035	11,600
AFP+US ANNUAL	31,000	10.985	1,500	0.127	11,500	<i>Dominated by AFP 6-MO</i>		
US 6-MO	31,100	10.988	1,600	0.130	12,100	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	31,500	11.021	1,900	0.163	11,900	600	0.031	18,100
<b>HCV</b>								
NO SURVEILLANCE	27,600	8.087						
AFP ANNUAL	28,500	8.128	900	0.042	22,000	900	0.042	22,000
US ANNUAL	28,600	8.128	1,000	0.042	24,400	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	28,900	8.141	1,300	0.054	24,300	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	29,000	8.146	1,400	0.059	23,100	400	0.017	25,700
US 6-MO	29,100	8.145	1,500	0.058	25,200	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	29,500	8.160	1,900	0.073	25,500	500	0.014	35,400
Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).								

distribution (approximating a similar number of slow-growing and fast-growing tumours) and two beta distributions (approximating a preponderance of slow-growing and fast-growing tumours, respectively). The results of these analyses are shown in *Table 58*.

The results that were pooled using a normal distribution are fairly close to those generated in the deterministic base case, although a minor increase in cost-effectiveness is apparent. This suggests that fast-growing tumours improve the cost-effectiveness of surveillance interventions to

an extent that slightly outweighs the negative effect of slow-growing tumours.

This conclusion is supported by the analyses that are weighted according to beta distributions. When slow-growing tumours predominate, people tend to live for longer (this is to be expected, as the natural history of the disease has effectively been slowed down), but the incremental benefit of surveillance is fairly slight. The analysis that simulates a preponderance of fast-growing tumours has the opposite characteristics: fewer QALYs are generated, on average, but the

**TABLE 57** Scenario analyses: cost–utility with very poor compliance (75% of appointments missed; 10% per annum of surveillance cohort drop out entirely)

Strategy	Cost (£)	Utility (QALYs)	Compared to NO SURVEILLANCE			Compared to next cheapest cost-effective strategy		
			Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)	Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)
<b>Mixed</b>								
NO SURVEILLANCE	26,900	9.021						
AFP ANNUAL	27,200	9.037	300	0.016	20,600	300	0.016	20,600
US ANNUAL	27,300	9.037	400	0.016	24,100	<i>Dominated by AFP ANNUAL</i>		
AFP 6-MO	27,300	9.042	500	0.020	24,700	100	0.004	26,000
US 6-MO	27,400	9.041	400	0.020	22,000	<i>Dominated by AFP 6-MO</i>		
AFP+US ANNUAL	27,400	9.043	500	0.021	23,600	<i>Ext. dom. by AFP 6-MO and AFP+US 6-MO</i>		
AFP+US 6-MO	27,500	9.048	600	0.026	24,500	200	0.006	33,800
<b>ALD</b>								
NO SURVEILLANCE	26,100	9.359						
AFP ANNUAL	26,400	9.370	300	0.011	24,300	300	0.011	24,300
US ANNUAL	26,400	9.370	300	0.011	30,100	<i>Dominated by AFP ANNUAL</i>		
AFP 6-MO	26,500	9.372	400	0.014	26,100	100	0.003	33,400
AFP+US ANNUAL	26,500	9.373	400	0.015	29,100	<i>Ext. dom. by AFP 6-MO and AFP+US 6-MO</i>		
US 6-MO	26,500	9.372	400	0.014	31,400	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	26,700	9.377	500	0.018	30,600	200	0.004	44,500
<b>HBV</b>								
NO SURVEILLANCE	29,600	10.858						
AFP ANNUAL	30,000	10.900	400	0.042	10,000	400	0.042	10,000
US ANNUAL	30,000	10.900	500	0.041	11,600	<i>Dominated by AFP ANNUAL</i>		
AFP 6-MO	30,100	10.910	500	0.052	10,200	100	0.010	11,200
US 6-MO	30,200	10.909	600	0.051	11,700	<i>Dominated by AFP 6-MO</i>		
AFP+US ANNUAL	30,200	10.914	600	0.056	11,300	<i>Ext. dom. by AFP 6-MO and AFP+US 6-MO</i>		
AFP+US 6-MO	30,300	10.925	800	0.067	11,400	200	0.015	15,400
<b>HCV</b>								
NO SURVEILLANCE	27,600	8.087						
AFP ANNUAL	28,000	8.106	400	0.019	22,000	400	0.019	22,000
US ANNUAL	28,100	8.106	500	0.019	24,200	<i>Dominated by AFP ANNUAL</i>		
AFP 6-MO	28,200	8.111	600	0.024	22,900	100	0.006	25,500
US 6-MO	28,200	8.111	600	0.024	24,800	<i>Dominated by AFP 6-MO</i>		
AFP+US ANNUAL	28,200	8.112	600	0.025	24,000	<i>Ext. dom. by AFP 6-MO and AFP+US 6-MO</i>		
AFP+US 6-MO	28,400	8.119	800	0.032	24,700	200	0.007	30,700
Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).								

incremental benefit of surveillance is noticeably greater. This is a predictable finding, since HCCs that develop rapidly are, in the model, unlikely to be detected at a treatable stage unless surveillance is efficient at identifying them.

In conclusion, the model may slightly underestimate the cost-effectiveness of surveillance, by adopting a single average growth rate. Given the relatively close agreement of these figures with the base case, we believe that any effect is likely to be minor, but a more

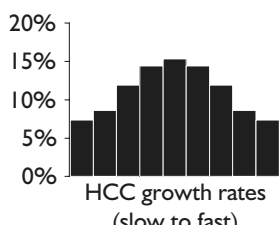
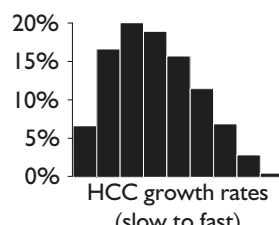
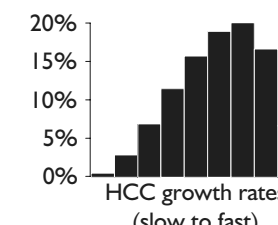
sophisticated model of individual tumour growth rates would be necessary to investigate this relationship in detail.

**Transplantation as the only surgical treatment option**

This scenario simplifies the decision problem by assuming that the only surgical treatment option available for HCC is liver transplantation.

The cost–utility results of this analysis are shown in *Table 59*.

TABLE 58 Scenario analyses: stratified tumour growth rates (mixed aetiology cohort)

Strategy	Cost (£)	Utility (QALYs)	Compared to NO SURVEILLANCE			Compared to next cheapest cost-effective strategy		
			Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)	Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)
<b>Normal<sup>a</sup></b>								
NO SURVEILLANCE	26,800	8.998						
AFP ANNUAL	28,300	9.072	1,500	0.074	20,300	1,500	0.074	20,300
US ANNUAL	28,600	9.072	1,800	0.074	24,700	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	29,100	9.091	2,300	0.093	24,400	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	29,300	9.109	2,500	0.111	22,200	1,000	0.037	26,100
US 6-MO	29,800	9.109	3,000	0.111	26,700	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	30,300	9.128	3,500	0.130	27,000	1,000	0.019	55,100
<b>More slow-growing tumours<sup>b</sup></b>								
NO SURVEILLANCE	27,000	9.038						
AFP ANNUAL	28,500	9.107	1,500	0.068	22,400	1,500	0.068	22,400
US ANNUAL	28,800	9.107	1,800	0.069	26,900	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	29,200	9.123	2,300	0.085	26,900	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	29,400	9.138	2,500	0.100	24,800	1,000	0.032	30,000
US 6-MO	29,900	9.139	3,000	0.101	29,500	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	30,400	9.154	3,500	0.116	30,200	1,000	0.016	65,000
<b>More fast-growing tumours<sup>c</sup></b>								
NO SURVEILLANCE	26,600	8.952						
AFP ANNUAL	28,100	9.034	1,500	0.082	18,000	1,500	0.082	18,000
US ANNUAL	28,400	9.033	1,800	0.081	22,200	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	28,900	9.055	2,200	0.104	21,700	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	29,100	9.078	2,500	0.126	19,600	1,000	0.043	22,700
US 6-MO	29,600	9.076	3,000	0.124	23,800	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	30,100	9.100	3,500	0.148	23,800	1,000	0.022	47,000
Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).								
<sup>a</sup> Strata weighted according to normal distribution:			<sup>b</sup> Strata weighted according to beta distribution ( $\alpha = 1.5$ ; $\beta = 2.5$ ):			<sup>c</sup> Strata weighted according to beta distribution ( $\alpha = 2.5$ ; $\beta = 1.5$ ):		
								

These results are very similar to the main cost-utility outputs, doubtless because only a small proportion of individuals receive resection in the base case. In each case, surveillance is very slightly more effective, and very slightly more cost-effective, than in the main analysis. This is entirely as one would expect, and merely suggests that OLT has marginally superior cost-effectiveness than resection.

#### More effective, more expensive ultrasound

This is a speculative analysis, which seeks to account for anticipated improvements in the performance of ultrasound imaging. The parameters were loosely based on what might be

expected if contrast-enhanced ultrasound (CEUS) were used in the surveillance of patients for HCC. Because it would have entailed substantial restructuring of the model to define new screening algorithms using CEUS in conjunction with unenhanced ultrasound, values approximating the performance of CEUS were substituted for the existing ultrasound parameters. Therefore, this scenario assumes that all ultrasound examinations are contrast enhanced.

There is no robust published evidence as to the sensitivity of CEUS for detecting HCCs, and none detailed enough to account for the impact of

**TABLE 59** Scenario analyses: cost–utility in transplant-only treatment scenario

Strategy	Cost (£)	Utility (QALYs)	Compared to NO SURVEILLANCE			Compared to next cheapest cost-effective strategy		
			Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)	Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)
<b>Mixed</b>								
NO SURVEILLANCE	26,900	9.022						
AFP ANNUAL	28,500	9.099	1,600	0.078	21,000	1,600	0.078	21,000
US ANNUAL	28,800	9.099	1,900	0.077	25,100	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	29,300	9.118	2,400	0.097	25,000	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	29,600	9.137	2,700	0.115	23,100	1,000	0.037	27,500
US 6-MO	30,000	9.136	3,100	0.114	27,400	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	30,600	9.155	3,700	0.133	27,800	1,000	0.018	58,100
<b>ALD</b>								
NO SURVEILLANCE	26,100	9.358						
AFP ANNUAL	27,500	9.410	1,300	0.052	25,700	1,300	0.052	25,700
US ANNUAL	27,800	9.410	1,700	0.052	32,400	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	28,200	9.423	2,100	0.064	32,100	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	28,300	9.434	2,200	0.076	29,100	900	0.024	36,300
US 6-MO	28,900	9.435	2,700	0.076	36,100	<i>Ext. dom. by AFP 6-MO and AFP+US 6-MO</i>		
AFP+US 6-MO	29,400	9.446	3,200	0.088	36,800	1,000	0.012	87,300
<b>HBV</b>								
NO SURVEILLANCE	29,600	10.865						
AFP ANNUAL	31,900	11.099	2,300	0.234	9,700	2,300	0.234	9,700
US ANNUAL	32,200	11.092	2,600	0.228	11,600	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	32,900	11.155	3,300	0.290	11,300	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	33,200	11.214	3,600	0.349	10,400	1,400	0.115	11,800
US 6-MO	33,800	11.204	4,200	0.339	12,300	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	34,600	11.269	5,000	0.404	12,300	1,300	0.055	24,000
<b>HCV</b>								
NO SURVEILLANCE	27,600	8.087						
AFP ANNUAL	29,600	8.175	2,000	0.088	22,800	2,000	0.088	22,800
US ANNUAL	29,800	8.174	2,200	0.087	25,400	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	30,400	8.197	2,800	0.110	25,600	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	30,800	8.217	3,200	0.130	24,500	1,200	0.043	28,000
US 6-MO	31,200	8.217	3,500	0.130	27,200	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	31,800	8.238	4,200	0.151	27,900	1,000	0.021	49,700
Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).								

tumour size. It should be stressed that preliminary studies reporting the sensitivity of the technique as around 95%<sup>444–447</sup> are irrelevant in this context, as they relate to characterisation (of known but unclassified nodules), rather than detection (of lesions that may or may not be present in a series of cirrhotic livers). One observational study has been published reporting the use of CEUS in a surveillance series;<sup>448</sup> however, the reference standard used to establish ‘true’ diagnoses (long-term follow-up, including biopsy and CT) was suboptimal. Moreover, it is difficult to draw any conclusions about the accuracy of individual tests from such series, as they cannot account for the possibility that correctly identified lesions were

missed in previous scans in the same patient. There is an urgent need for well-designed studies, measuring the sensitivity of CEUS for detecting HCC in cirrhotic livers against a reliable reference standard (ideally, explant pathology in patients receiving OLT for liver failure).

For this scenario, in the absence of any relevant evidence, an increment was applied to the existing ultrasound sensitivity parameters. This increment was equivalent to assuming that, in the study informing the ultrasound parameter estimates,<sup>256</sup> CEUS would have resulted in half as many false-negative findings in patients with tumours. This equates to a sensitivity of 55.4%, 64.3% and 87.5%

TABLE 60 Scenario analyses: cost–utility with more effective, more expensive ultrasound

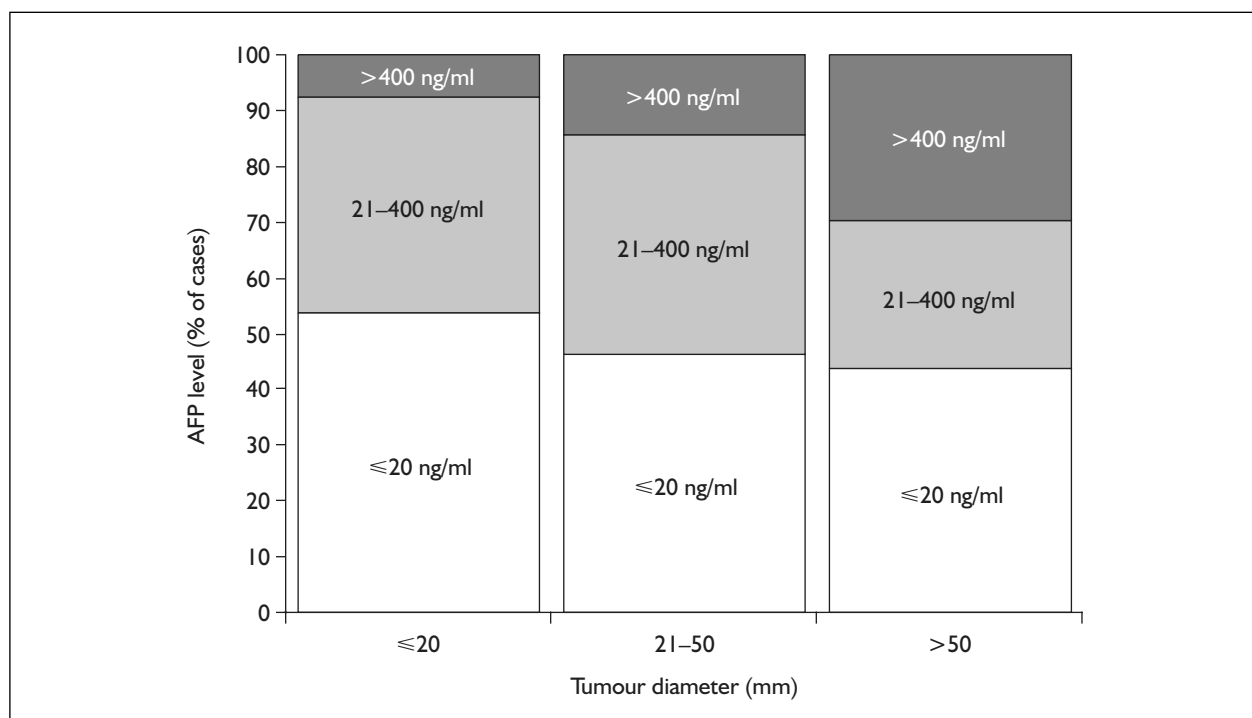
Strategy	Cost (£)	Utility (QALYs)	Compared to NO SURVEILLANCE			Compared to next cheapest cost-effective strategy		
			Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)	Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)
<b>Mixed</b>								
NO SURVEILLANCE	26,900	9.021						
AFP ANNUAL	29,400	9.135	2,500	0.113	22,000	2,500	0.113	22,000
AFP 6-MO	30,300	9.162	3,500	0.140	24,600	1,000	0.027	35,800
US ANNUAL	30,800	9.155	3,900	0.134	29,000	<i>Dominated by AFP 6-MO</i>		
AFP+US ANNUAL	30,900	9.159	4,000	0.137	29,300	<i>Dominated by AFP 6-MO</i>		
US 6-MO	32,300	9.172	5,400	0.151	36,000	<i>Ext. dom. by AFP 6-MO and AFP+US 6-MO</i>		
AFP+US 6-MO	32,500	9.174	5,600	0.152	36,800	2,100	0.012	177,700
<b>ALD</b>								
NO SURVEILLANCE	26,100	9.359						
AFP ANNUAL	28,200	9.435	2,000	0.076	26,600	2,000	0.076	26,600
AFP 6-MO	29,000	9.453	2,900	0.094	30,700	900	0.018	48,400
US ANNUAL	29,500	9.449	3,400	0.090	37,900	<i>Dominated by AFP 6-MO</i>		
AFP+US ANNUAL	29,600	9.451	3,500	0.092	38,300	<i>Dominated by AFP 6-MO</i>		
US 6-MO	31,100	9.460	4,900	0.101	49,000	<i>Ext. dom. by AFP 6-MO and AFP+US 6-MO</i>		
AFP+US 6-MO	31,200	9.460	5,100	0.102	50,100	2,200	0.008	292,000
<b>HBV</b>								
NO SURVEILLANCE	29,600	10.858						
AFP ANNUAL	33,000	11.187	3,400	0.329	10,400	3,400	0.329	10,400
AFP 6-MO	34,200	11.269	4,600	0.411	11,300	1,200	0.082	14,900
US ANNUAL	34,700	11.247	5,100	0.389	13,200	<i>Dominated by AFP 6-MO</i>		
AFP+US ANNUAL	34,900	11.257	5,300	0.399	13,300	<i>Dominated by AFP 6-MO</i>		
US 6-MO	36,600	11.304	7,100	0.446	15,800	<i>Ext. dom. by AFP 6-MO and AFP+US 6-MO</i>		
AFP+US 6-MO	36,800	11.309	7,300	0.451	16,100	2,600	0.040	65,000
<b>HCV</b>								
NO SURVEILLANCE	27,600	8.087						
AFP ANNUAL	30,700	8.216	3,100	0.130	23,600	3,100	0.130	23,600
AFP 6-MO	31,700	8.247	4,100	0.160	25,900	1,100	0.031	35,500
US ANNUAL	32,000	8.240	4,400	0.153	28,800	<i>Dominated by AFP 6-MO</i>		
AFP+US ANNUAL	32,200	8.244	4,600	0.157	29,200	<i>Dominated by AFP 6-MO</i>		
US 6-MO	33,500	8.259	5,900	0.172	34,400	<i>Ext. dom. by AFP 6-MO and AFP+US 6-MO</i>		
AFP+US 6-MO	33,700	8.261	6,100	0.174	35,000	1,900	0.014	142,900

Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).

in small, medium and large HCCs, respectively. The specificity of the test was not altered, as the evidence base is insufficient to support even the broadest assumption; it is possible that CEUS will reduce false-positive findings, but it is perhaps as likely that more non-cancerous nodules will cause suspicion under these circumstances. The unit cost of ultrasound was raised, to account for the extra expense entailed in performing these tests. This was approximated by assuming that operator time increases by 50% and the contrast agent costs £50 per test, amounting to a total of £125 per test.

The cost–utility results of this scenario analysis are shown in Table 60.

For the reasons discussed above, this exploratory scenario should not be interpreted as a robust, evidence-based estimation of the cost–utility of CEUS. Nevertheless, it highlights one very important characteristic of the relationship between the kinds of surveillance strategy that will increasingly be considered as imaging technology advances. Although, in this scenario, ANNUAL US is substantially more effective than ANNUAL AFP TRIAGE (generating as many as 0.06 extra QALYs in



**FIGURE 22** Alternative AFP data: secretion level according to tumour size (data extracted from Farinati et al., 2006<sup>329</sup>)

the HBV cohort), the extra costs entailed are sufficient to make it more expensive than 6-MONTHLY AFP TRIAGE. As a result, the model predicts that, given the choice of a relatively expensive, relatively sensitive test versus a relatively inexpensive, relatively insensitive test performed at twice the frequency, the latter will detect more tumours, and do so at a lower cost. This possibility should be borne in mind; although the benefit of more sensitive imaging technology is obvious, it will always be worth questioning whether the resources demanded by innovative techniques might be more effectively deployed in using existing technology more often. These speculative results are insufficient to establish whether this pattern would be realised with the wider use of CEUS; however, this analysis demonstrates that, in this and other areas, the danger plainly exists.

**Alternative AFP sensitivity data**

While we were in the final stages of preparing this report, a comprehensive study reporting the diagnostic accuracy of AFP assay in a consecutive series of more than 1000 Italian HCC patients was published by Farinati and co-workers.<sup>329</sup> Their data (see Figure 22) suggest that the estimates adopted in the present model (see pp. 43–44) may slightly underestimate the proportion of HCCs that secrete low levels of AFP (<20 ng/ml). Although these new data were published too late to be integrated throughout the analyses, a

scenario analysis was performed in which the new values are used, to investigate the impact that this evidence might be expected to have on the present findings. The cost–utility outputs are shown in Table 61.

This alteration has little obvious effect on the base-case results. The effectiveness of AFP-based surveillance diminishes very slightly (by 0.003 QALYs in both 6-MONTHLY AFP TRIAGE and ANNUAL AFP TRIAGE in the mixed aetiology cohort). This is a reflection of a raised false-negative rate caused by the larger proportion of non-secreting tumours. In contrast, the effectiveness of AFP+US strategies rises somewhat. This is because the number of high-AFP-secreting tumours is slightly higher in the new data, leading to increased detection of HCCs (especially medium-sized ones).

The most notable difference from the main analysis comes in the relative benefit of strategies that make primary use of AFP compared with those that rely on ultrasound. In the base case, ultrasound surveillance is frequently dominated by AFP TRIAGE surveillance at the same interval (that is, ultrasound is more costly and less effective than AFP TRIAGE). In the reanalyses with new AFP data, ultrasound is consistently more effective than AFP TRIAGE, although the extra costs incurred in ultrasound-led surveillance always outweigh the

**TABLE 61** Scenario analyses: cost–utility when adopting alternative AFP sensitivity data

Strategy	Cost (£)	Utility (QALYs)	Compared to NO SURVEILLANCE			Compared to next cheapest cost-effective strategy		
			Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)	Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)
<b>Mixed</b>								
NO SURVEILLANCE	26,900	9.021						
AFP ANNUAL	28,300	9.093	1,400	0.071	20,300	1,400	0.071	20,300
AFP 6-MO	28,800	9.096	1,900	0.074	25,000	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
US ANNUAL	29,200	9.116	2,300	0.094	24,600	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP+US ANNUAL	29,300	9.128	2,400	0.106	22,500	900	0.035	27,100
US 6-MO	29,900	9.131	3,000	0.110	27,400	<i>Ext. dom. by AFP 6-MO and AFP+US 6-MO</i>		
AFP+US 6-MO	30,400	9.149	3,500	0.128	27,600	1,100	0.022	52,400
<b>ALD</b>								
NO SURVEILLANCE	26,100	9.359						
AFP ANNUAL	27,300	9.407	1,200	0.049	24,300	1,200	0.049	24,300
AFP 6-MO	27,700	9.410	1,600	0.051	31,700	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
US ANNUAL	28,100	9.423	2,000	0.064	31,000	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP+US ANNUAL	28,100	9.431	2,000	0.072	27,700	800	0.024	34,700
US 6-MO	28,800	9.434	2,600	0.075	35,400	<i>Ext. dom. by AFP 6-MO and AFP+US 6-MO</i>		
AFP+US 6-MO	29,200	9.446	3,100	0.087	35,700	1,100	0.015	75,500
<b>HBV</b>								
NO SURVEILLANCE	29,600	10.858						
AFP ANNUAL	31,600	11.058	2,000	0.200	10,000	2,000	0.200	10,000
AFP 6-MO	32,100	11.066	2,500	0.208	12,100	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
US ANNUAL	32,700	11.123	3,100	0.265	11,800	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP+US ANNUAL	32,800	11.156	3,200	0.298	10,900	1,200	0.098	12,600
US 6-MO	33,600	11.164	4,000	0.306	13,100	<i>Ext. dom. by AFP 6-MO and AFP+US 6-MO</i>		
AFP+US 6-MO	34,300	11.219	4,700	0.361	13,000	1,400	0.063	23,000
<b>HCV</b>								
NO SURVEILLANCE	27,600	8.087						
AFP ANNUAL	29,400	8.168	1,800	0.082	21,700	1,800	0.082	21,700
AFP 6-MO	29,700	8.172	2,100	0.085	25,000	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
US ANNUAL	30,300	8.195	2,700	0.108	24,800	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP+US ANNUAL	30,500	8.209	2,900	0.122	23,400	1,100	0.040	27,000
US 6-MO	31,000	8.213	3,400	0.126	26,700	<i>Ext. dom. by AFP 6-MO and AFP+US 6-MO</i>		
AFP+US 6-MO	31,600	8.234	4,000	0.147	27,300	1,200	0.025	45,700

Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).

benefit, and AFP-led and combined strategies remain the most cost-effective options.

#### Longer waiting times for liver transplantation

Liver transplantation is one of the two main treatments for HCCs discovered while they are still small or medium sized (<5 cm diameter). Clearly, the longer that people with compensated cirrhosis and HCC tumours are on a transplant waiting list, the greater the chance that either their cirrhosis or their tumour may progress to the point that they are no longer eligible for a transplant. In theory, therefore, the average length of time

waiting for a liver transplant may impact on the effectiveness and cost-effectiveness of any surveillance programme.

However, as *Table 62* shows, even doubling the median time on the transplant waiting list (from 72 to 144 days) only alters the various ICERs by a very small amount (£100–700).

#### Detailed one-way sensitivity analyses

In the following sensitivity analyses, related (usually correlated) parameters of interest are varied in the same direction while all other values,

**TABLE 62** Scenario analyses: cost–utility with doubled transplant waiting time (median 144 days)

Strategy	Cost (£)	Utility (QALYs)	Compared to NO SURVEILLANCE			Compared to next cheapest cost-effective strategy		
			Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)	Incr. cost (£)	Incr. utility (QALYs)	Incr. £/QALY (ICER)
<b>Mixed</b>								
NO SURVEILLANCE	26,800	8.980						
AFP ANNUAL	28,300	9.051	1,500	0.071	20,700	1,500	0.071	20,700
US ANNUAL	28,600	9.050	1,800	0.070	25,300	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	29,000	9.068	2,200	0.088	25,000	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	29,200	9.085	2,400	0.105	22,800	900	0.034	27,300
US 6-MO	29,700	9.084	2,900	0.104	27,700	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	30,200	9.102	3,400	0.122	28,000	1,000	0.017	60,500
<b>ALD</b>								
NO SURVEILLANCE	26,100	9.325						
AFP ANNUAL	27,200	9.373	1,200	0.048	24,700	1,200	0.048	24,700
US ANNUAL	27,600	9.373	1,500	0.048	32,200	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	28,000	9.385	1,900	0.060	31,600	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	28,100	9.397	2,000	0.071	28,100	800	0.023	35,100
US 6-MO	28,600	9.396	2,500	0.071	35,900	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	29,000	9.408	3,000	0.083	36,200	1,000	0.011	88,700
<b>HBV</b>								
NO SURVEILLANCE	29,100	10.719						
AFP ANNUAL	31,200	10.917	2,000	0.198	10,300	2,000	0.198	10,300
US ANNUAL	31,500	10.913	2,400	0.194	12,400	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	32,100	10.964	3,000	0.246	12,100	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	32,400	11.013	3,300	0.294	11,100	1,200	0.096	12,800
US 6-MO	33,000	11.006	3,800	0.287	13,300	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	33,600	11.058	4,500	0.340	13,300	1,300	0.046	27,400
<b>HCV</b>								
NO SURVEILLANCE	27,700	8.054						
AFP ANNUAL	29,500	8.136	1,800	0.081	22,000	1,800	0.081	22,000
US ANNUAL	29,700	8.135	2,000	0.081	25,100	<i>Dominated by AFP ANNUAL</i>		
AFP+US ANNUAL	30,200	8.156	2,500	0.102	25,100	<i>Ext. dom. by AFP ANNUAL and AFP 6-MO</i>		
AFP 6-MO	30,500	8.175	2,900	0.121	23,700	1,100	0.040	27,100
US 6-MO	30,900	8.174	3,200	0.120	26,800	<i>Dominated by AFP 6-MO</i>		
AFP+US 6-MO	31,500	8.195	3,800	0.141	27,300	1,000	0.019	50,100
Mixed aetiology cohort weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).								

which may themselves be subject to uncertainty, are held at their base-case values. In contrast to the simple one-way analyses presented above, these analyses show the effect of the parameters of interest on all surveillance strategies.

These analyses have been conducted over very wide ranges of the selected parameters, either because of particular uncertainty about where the true value might lie (e.g. compliance with surveillance, average tumour growth rates), because the research literature-derived values of these parameters may not reflect current practice or technological developments (e.g. sensitivity of ultrasound), or because they are critical to some of the conclusions that differ from currently

recommended surveillance strategies (e.g. the low cost of AFP testing has probably played a part in the finding that surveillance with AFP as the initial test is always cheaper and always more cost-effective than surveillance with ultrasound at the same frequency).

**Compliance**

In this analysis, the two parameters defining the probability that screening appointments will be met were varied over a range of correlated values. The likelihood of any individual test cycle being performed ranged from 25 to 100% and, simultaneously, the proportion of the cohort dropping out of the programme entirely was varied from 10% per annum to nil.



The results of this analysis are predictable: increasingly reliable patient compliance is associated with higher effectiveness (*Figure 23*). When very poor patient compliance is simulated, the small effect of surveillance is equivalent to that which might be expected from a cohort with a small number of regular attendees and a small number of lucky individuals whose infrequent visits happen to coincide with early subclinical tumour growth.

Equally foreseeable is the effect that compliance has on the relationship between strategies. In particular, under conditions of poor patient compliance, the marginal benefit associated with 6-monthly surveillance programmes, compared with annual strategies, is fairly slight, and the strategies gradually diverge as patient compliance improves. It is clear that the expected benefits of frequent surveillance should be contingent upon the probability that any scheduled test will actually be undertaken.

#### **Tumour growth rate**

In addition to the stratified scenario analyses, above, which investigate the impact of variation in tumour growth rates, this one-way analysis examines the effect of varying the average rate at which all tumours in the base case of the model are assumed to grow.

*Figure 24* shows the effectiveness (QALY) outputs that the model generates as tumour growth rates are varied over a range that represents a volume doubling time of 80 to 203 days. As would be expected, raising tumour growth rate effectively accelerates natural history and leads to smaller QALY outputs. In contrast, if slow-growing tumours are assumed to be the norm, the cohort generates larger QALYs, on average. It is also noticeable that, as progressively slower tumour growth rates are assumed, the effectiveness of all surveillance strategies converges, indicating a decreased marginal benefit. These findings are entirely consistent with the results of the stratified scenario analyses.

#### **Sensitivity of ultrasound**

In this analysis, the parameters defining the sensitivity of ultrasound for detecting tumours were simultaneously varied over a range of correlated values from 5 to 50%, 10 to 75% and 50 to 100% for small, medium and large HCCs, respectively.

As one would expect, increasing ultrasound sensitivity leads to improved effectiveness in all

surveillance strategies (*Figure 25*). (It should be remembered that, according to the screening algorithms, the strategies that use AFP assay as a primary test also rely on ultrasound to confirm initial findings.) It is also predictable that, on the whole, the ultrasound-led strategies benefit most from increasing detection rates.

Although the absolute QALY outputs are very different across individual aetiologies, the interstrategy relationships are extremely similar (consequently, this homogeneity is reflected in the pooled cohort). At both annual and 6-monthly frequencies, ultrasound surveillance becomes more effective than AFP TRIAGE surveillance when it can be assumed that ultrasound is at least sensitive enough to detect one in five small tumours, one in three medium tumours and two in three large tumours.

It should be emphasised that this analysis overlooks cost considerations. Given the substantial difference in unit cost between AFP assay and ultrasound, it cannot be assumed that superior effectiveness would always come at an acceptable cost. To investigate this question, *Figure 26* shows the cost-effectiveness of surveillance, expressed as net monetary benefit (using a conventional UK WTP threshold of £30,000 per QALY), relative to increasing ultrasound sensitivity. This metric captures the essential cost-effectiveness of each strategy: the higher the net monetary benefit, the more cost-effective the strategy.

The broad shape of cost-effectiveness results reflects the effectiveness-only outputs: increasing ultrasound sensitivity leads to improved cost-effectiveness in all surveillance strategies, most notably in ultrasound-led strategies. However, it is only in the HBV cohort that ultrasound becomes more cost-effective than AFP TRIAGE surveillance at the same frequencies. This is because the AFP TRIAGE strategies also benefit from increased ultrasound sensitivity in cases where AFP level raises suspicion of HCC, while retaining the favourable cost implications of limiting use of imaging.

It is notable that, in the ALD cohort, 6-MONTHLY US and 6-MONTHLY AFP+US never exceed the net monetary benefit (assuming a WTP of £30,000 per QALY) estimated for NO SURVEILLANCE. This suggests that, no matter how sensitive ultrasound detection is assumed to be, one would have to be prepared to pay more than £30,000 per QALY gained before it could be considered cost-effective

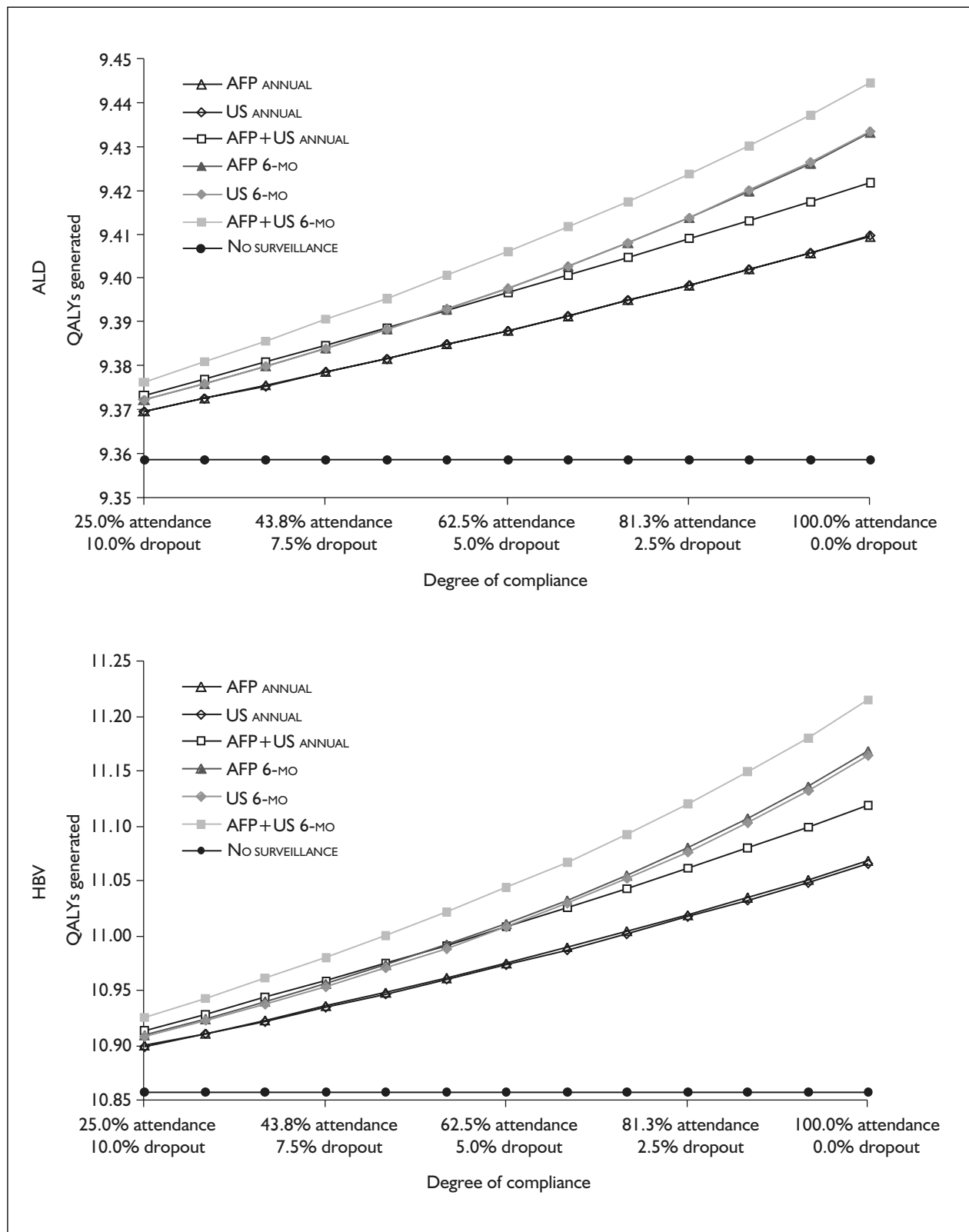
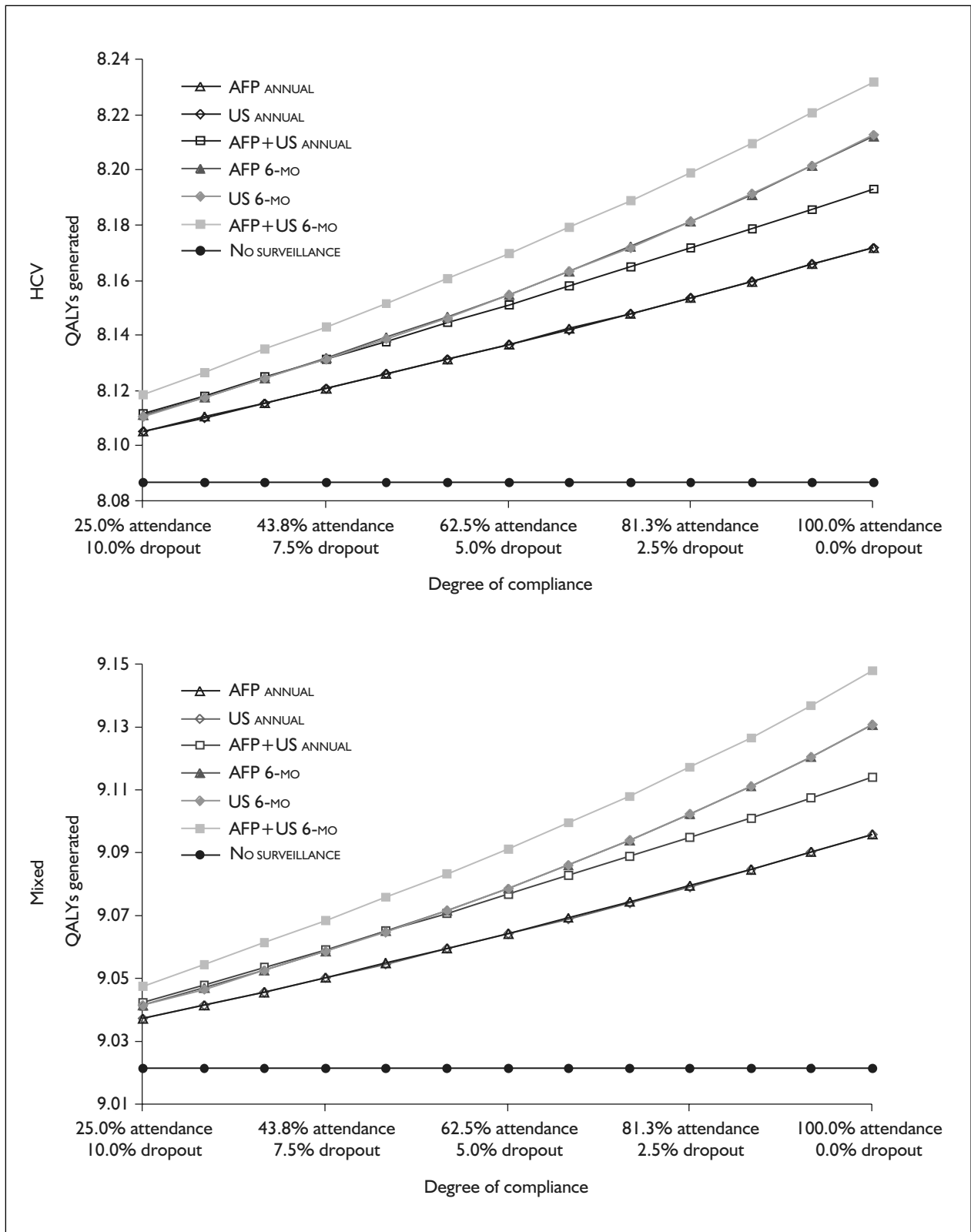


FIGURE 23 Detailed one-way sensitivity analyses: effectiveness of surveillance relative to compliance of individuals in programme



**FIGURE 23 (continued)** Detailed one-way sensitivity analyses: effectiveness of surveillance relative to compliance of individuals in programme

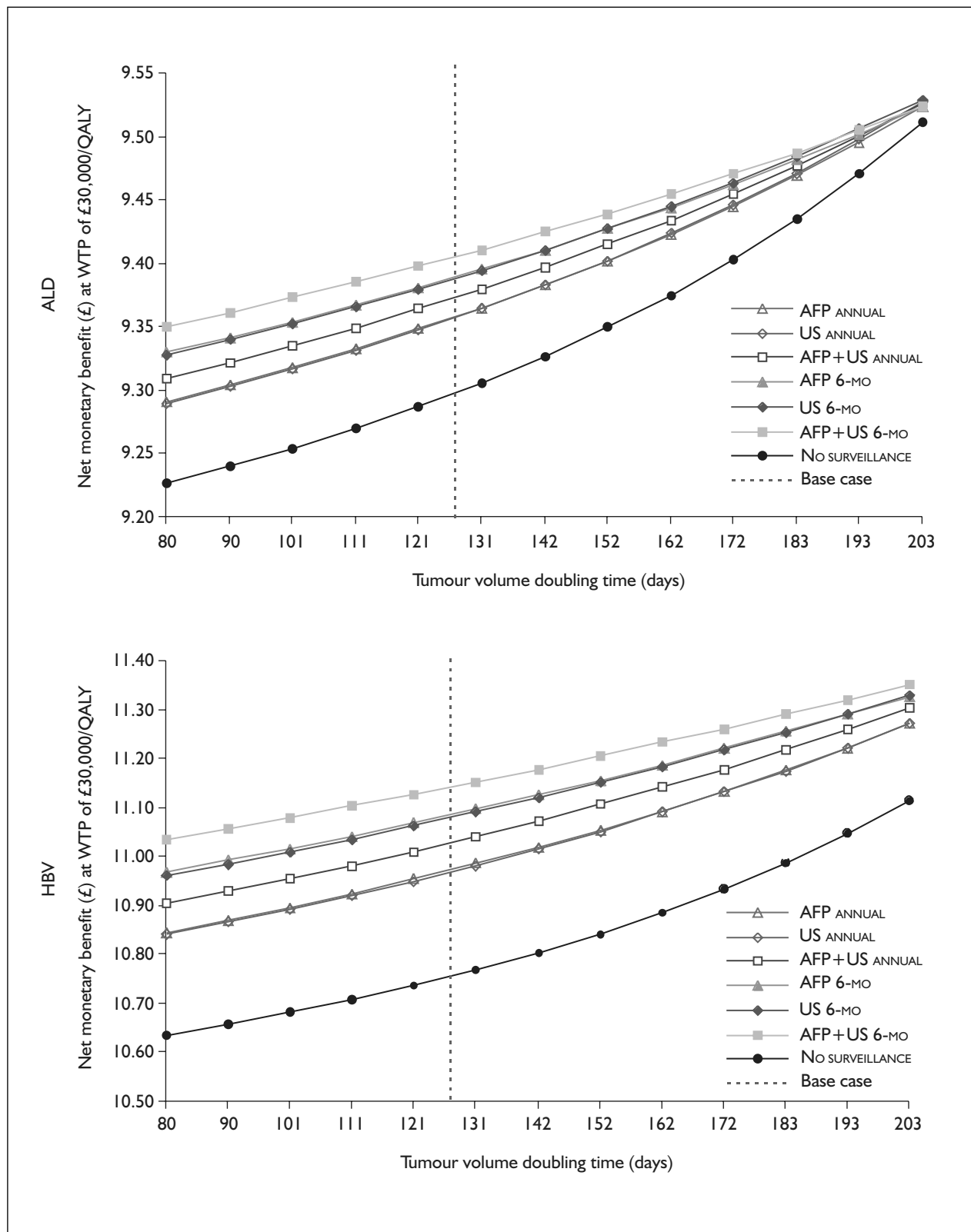


FIGURE 24 Detailed one-way sensitivity analyses: effectiveness of surveillance relative to tumour growth rate

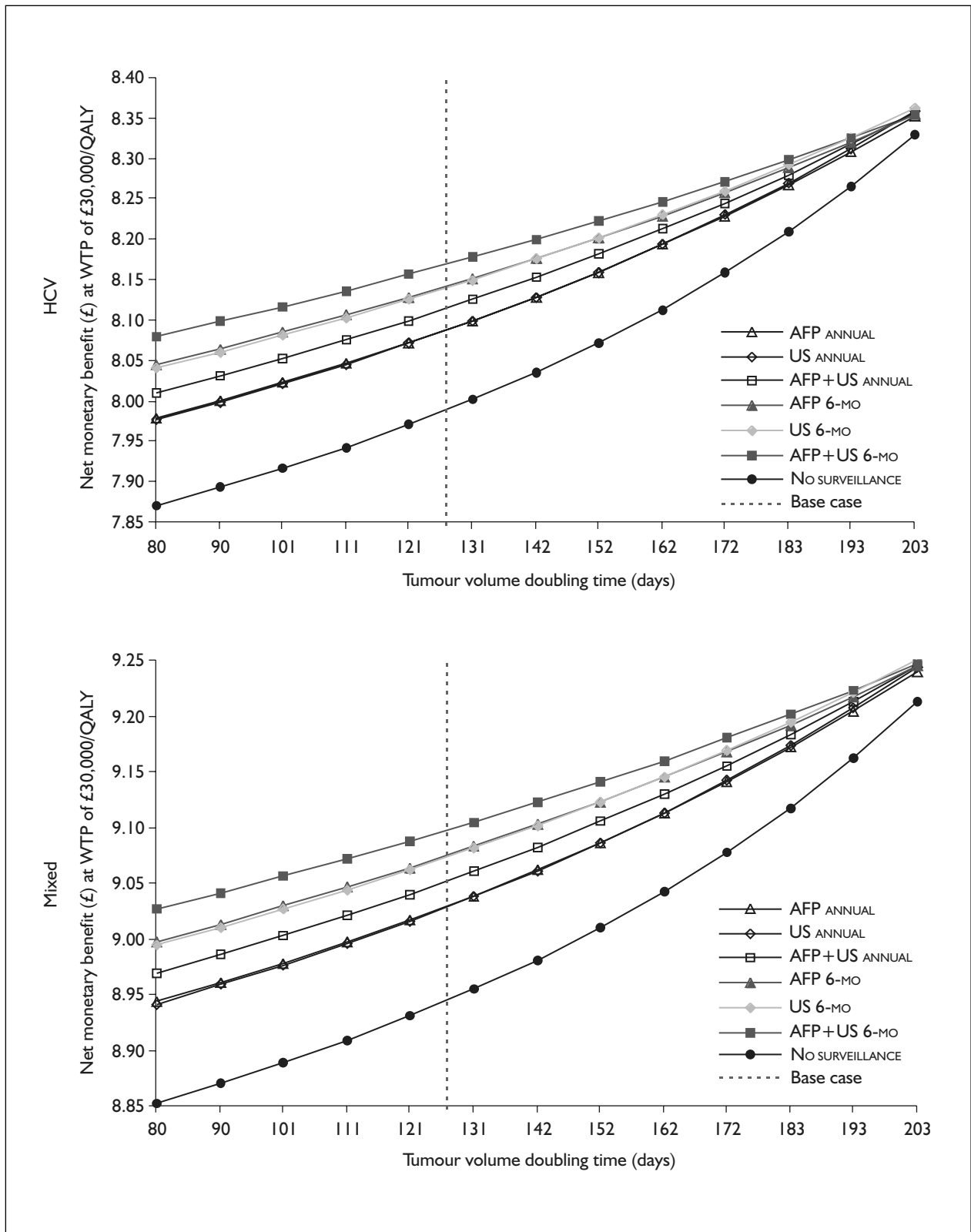
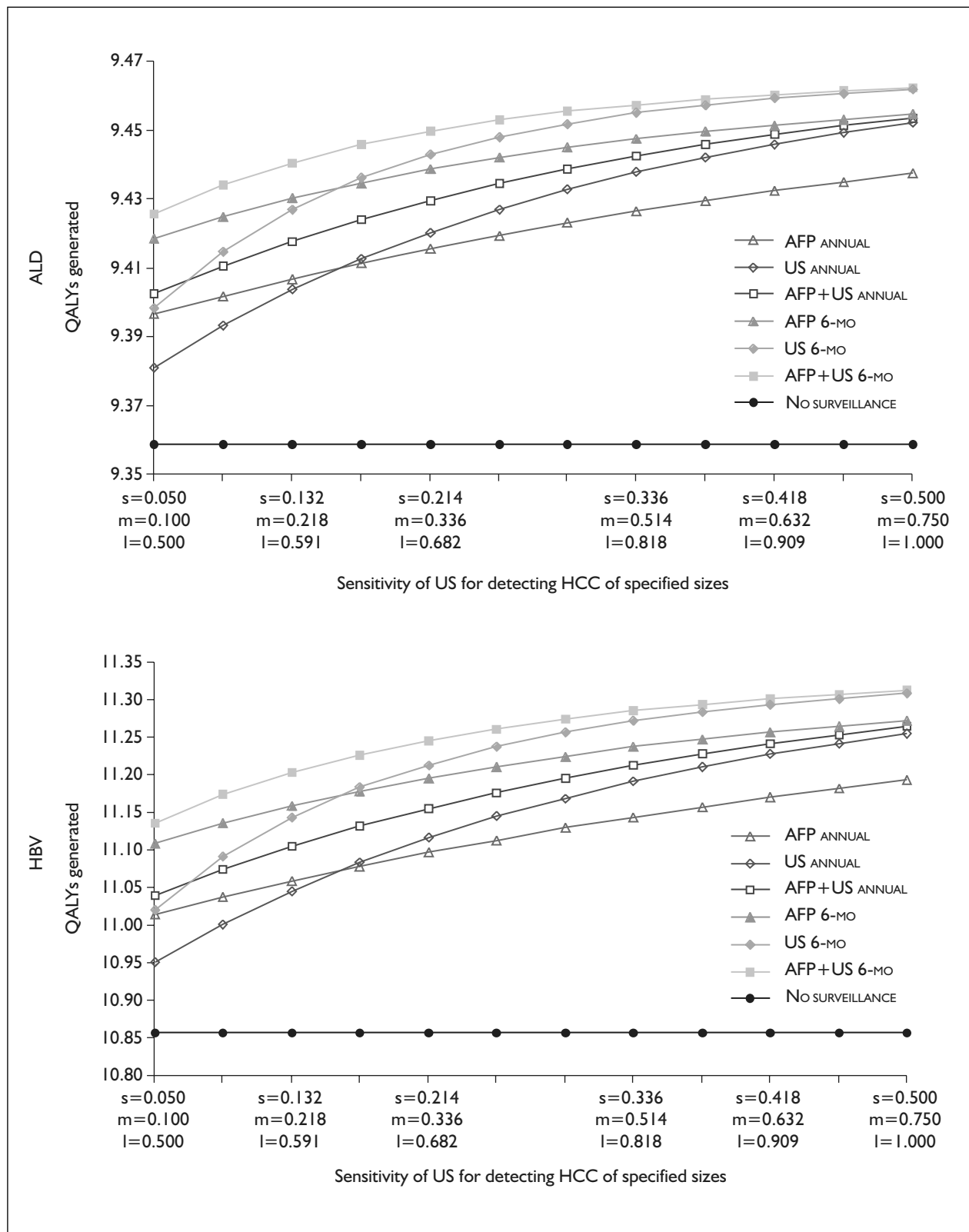
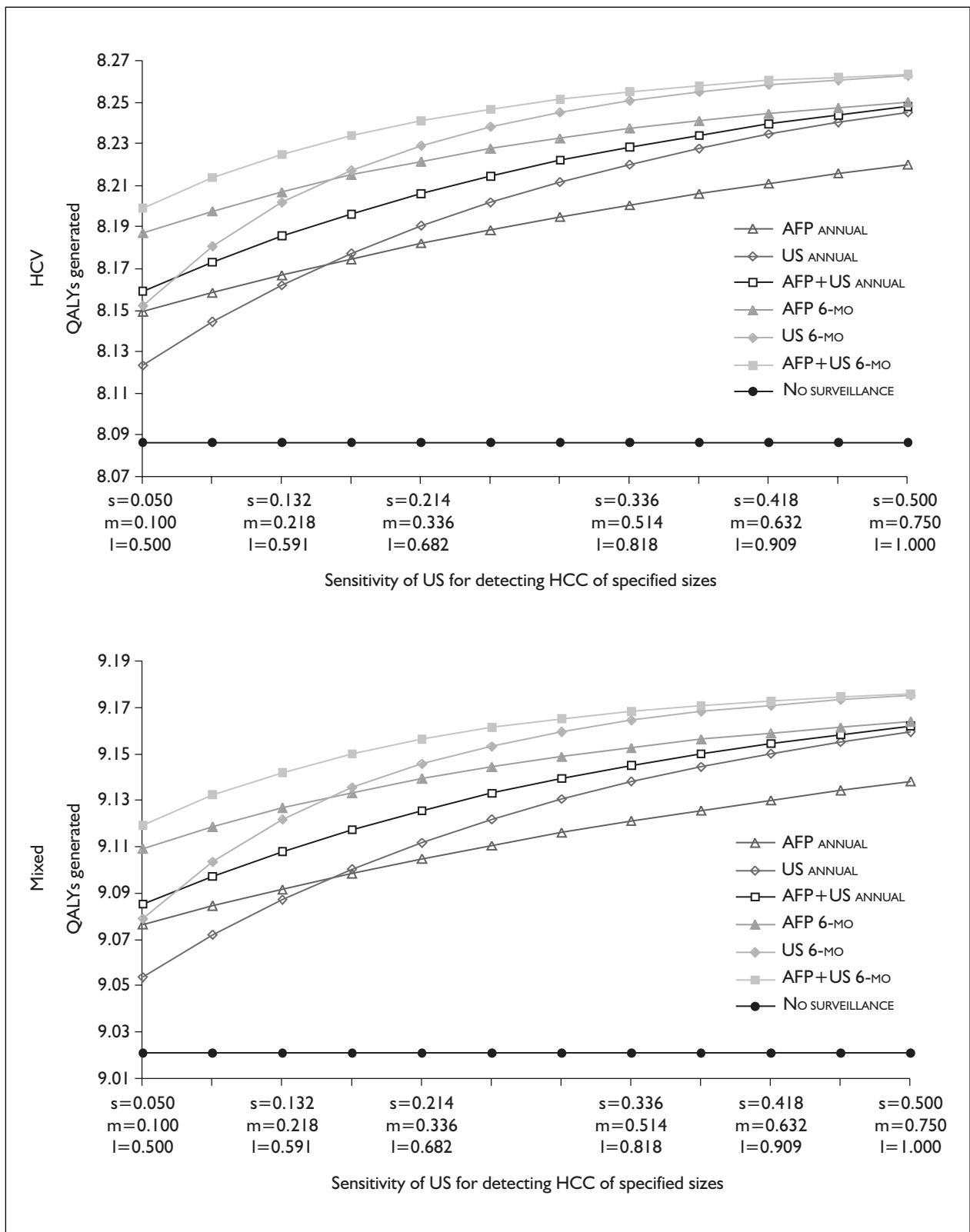


FIGURE 24 (continued) Detailed one-way sensitivity analyses: effectiveness of surveillance relative to tumour growth rate



**FIGURE 25** Detailed one-way sensitivity analyses: effectiveness of surveillance relative to sensitivity of ultrasound. *l*, sensitivity for large HCC; *m*, sensitivity for medium HCC; *s*, sensitivity for small HCC.



**FIGURE 25 (continued)** Detailed one-way sensitivity analyses: effectiveness of surveillance relative to sensitivity of ultrasound. *l*, sensitivity for large HCC; *m*, sensitivity for medium HCC; *s*, sensitivity for small HCC.

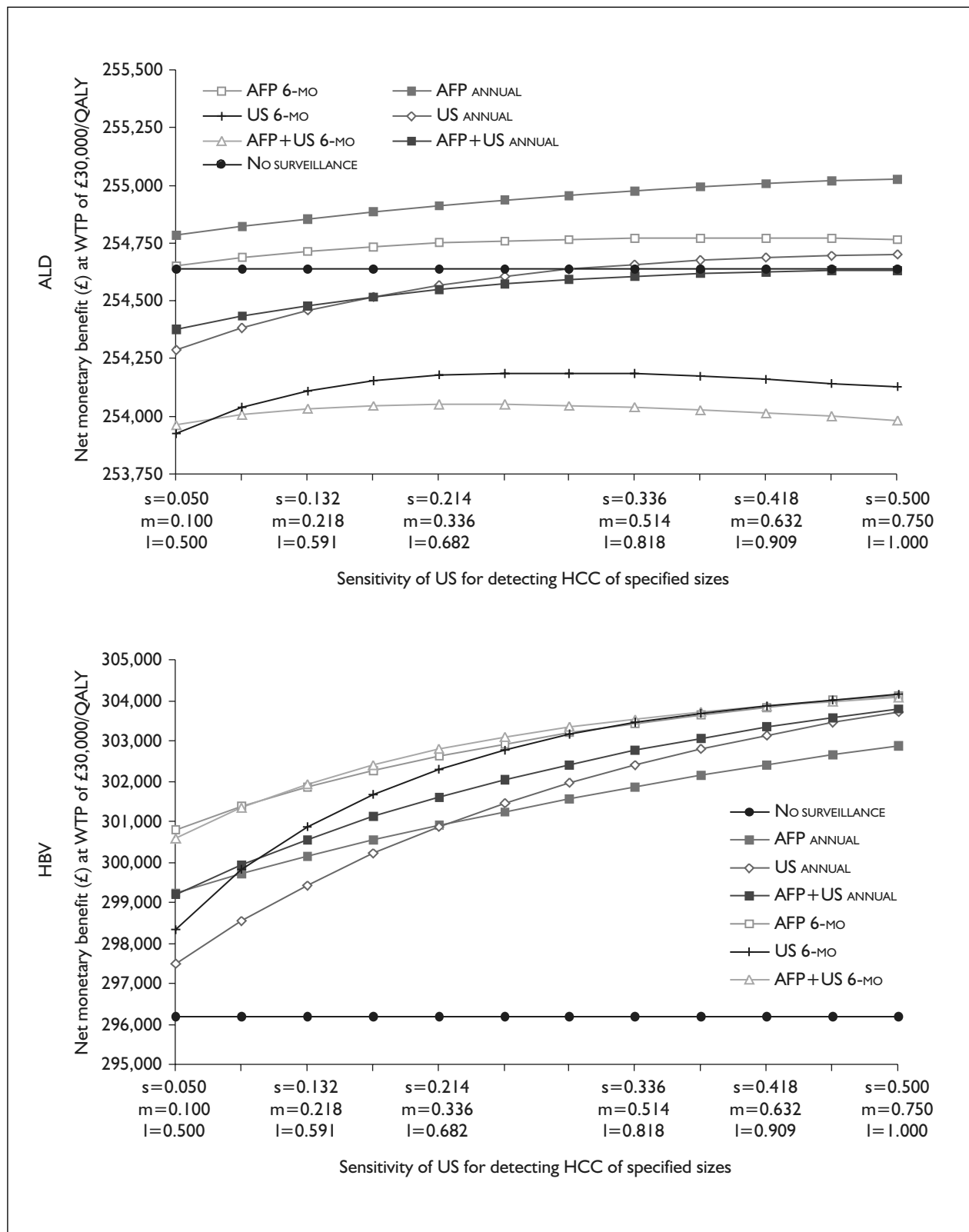


FIGURE 26 Detailed one-way sensitivity analyses: cost-effectiveness of surveillance relative to sensitivity of ultrasound



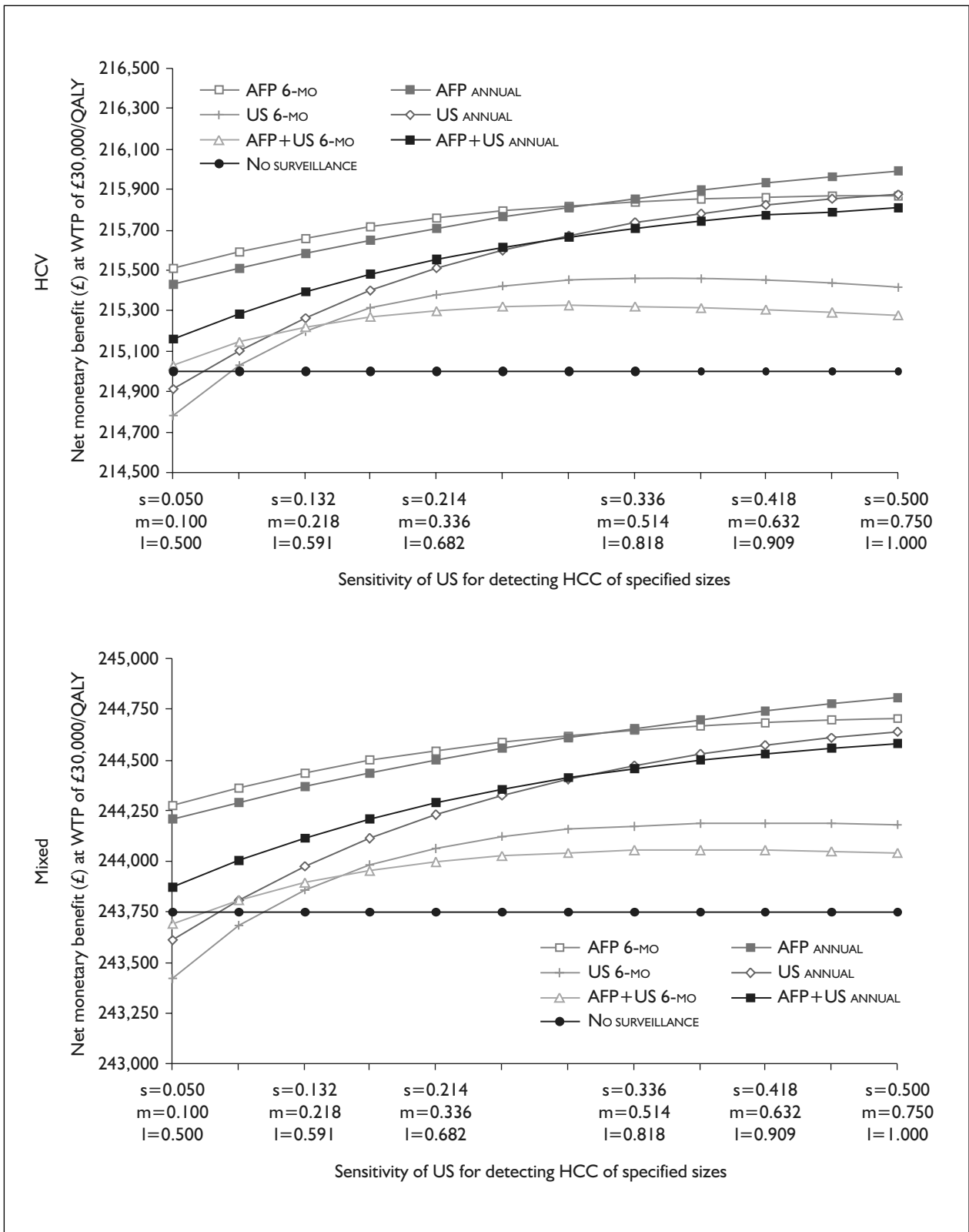


FIGURE 26 (continued) Detailed one-way sensitivity analyses: cost-effectiveness of surveillance relative to sensitivity of ultrasound

to offer people with ALD-related cirrhosis a routine ultrasound on a 6-monthly basis.

One unexpected feature, most apparent in the ALD and HCV plots, is a tendency for cost-effectiveness to decrease as sensitivity reaches very high levels in the two most expensive strategies (6-MONTHLY US and 6-MONTHLY AFP+US). Investigation of this characteristic has demonstrated that it is due to the effects of discounting, since undiscounted threshold analyses (not shown) preserve the trend for cost-effectiveness to increase as ultrasound sensitivity rises.

This finding is easily understood. Increasing ultrasound sensitivity effectively raises the probability that a tumour will be promptly detected; thus, the more effective the surveillance, the earlier costly interventions (most notably OLT) take place. When these costs are discounted, parameter sets that produce very similar effectiveness outputs may decline in cost-effectiveness because costs are being accrued at a progressively earlier stage in the simulated treatment pathway. The result of this phenomenon is that, to retain increasing cost-effectiveness in discounted analyses, surveillance strategies must find a higher number of treatable tumours, not just a similar number earlier.

The phenomenon is not apparent in HBV because, in this cohort, the absolute advantage of detection followed by OLT is so great that the improved detection of even a tiny number of additional tumours will always be cost-effective, within any except the most extremely implausible range of ultrasound sensitivity.

Taken together, the effectiveness and cost-effectiveness outputs of the model, when considered as a function of ultrasound sensitivity, depict a credible scenario. It only takes a slight increase in ultrasound sensitivity above the model's base-case values to render ultrasound-led screening more effective than AFP TRIAGE. However, AFP TRIAGE strategies are cheaper and also benefit from increased ultrasound sensitivity, so it is only in the HBV cohort that ultrasound-led surveillance programmes exceed the cost-effectiveness of AFP TRIAGE at the same frequencies as ultrasound sensitivity is increased.

#### **Cost of AFP test**

In the base case, a cost value for AFP assay of £4 per test was used, and varied from £2 to £8 in

sensitivity analyses. This choice was based on data obtained from a number of NHS clinical biochemistry departments (see the section 'Unit costs of surveillance programme, diagnostic tests and treatments', p. 52). Results of the one-way sensitivity analysis suggest that this is not an important area of uncertainty in the model. However, this cost does not take into account any resource use accompanying the performance of the test (e.g. consultation time with a hepatology nurse, consultant or general practitioner). Therefore, a threshold analysis was performed on the cost of AFP, which examines model outputs as this unit cost is increased.

Because this analysis examines the impact of a cost input, it is uninformative to concentrate on effectiveness outputs alone. Accordingly, cost-effectiveness, expressed as net monetary benefit at a WTP threshold of £30,000 per QALY, was plotted as a function of the parameter of interest.

When the cost of AFP assay exceeds approximately £35, 6-MONTHLY AFP TRIAGE becomes less cost-effective than 6-MONTHLY US. At a slightly higher threshold, around £43 per test, ANNUAL AFP TRIAGE becomes less cost-effective than ANNUAL US. Because equal numbers of AFP tests are used in the AFP TRIAGE and AFP+US algorithms, the marginal difference between strategies based on them is negligible (*Figure 27*).

It is important to remember that, owing to the one-way nature of analyses such as this one, all model inputs other than the parameter of interest are held constant during the calculation of these outputs. In the present instance, it might be extremely important that the cost of ultrasound has not been varied, especially as regards any inferences that might be drawn about the relative benefits of AFP TRIAGE strategies versus ultrasound-led surveillance. Although one might argue that the base-case parameters underestimate the true cost of AFP assay, it is less likely that the relationship between the two tests has been misrepresented (i.e. it is pretty certain that the cost of an ultrasound examination is greater than the cost of an AFP assay). For this reason, an indication of the estimated cost of ultrasound (£50 per scan) is provided in the graphs; outputs above this level can only be considered valid if one is happy to assume that the base cost of AFP assay exceeds the base cost of ultrasound.

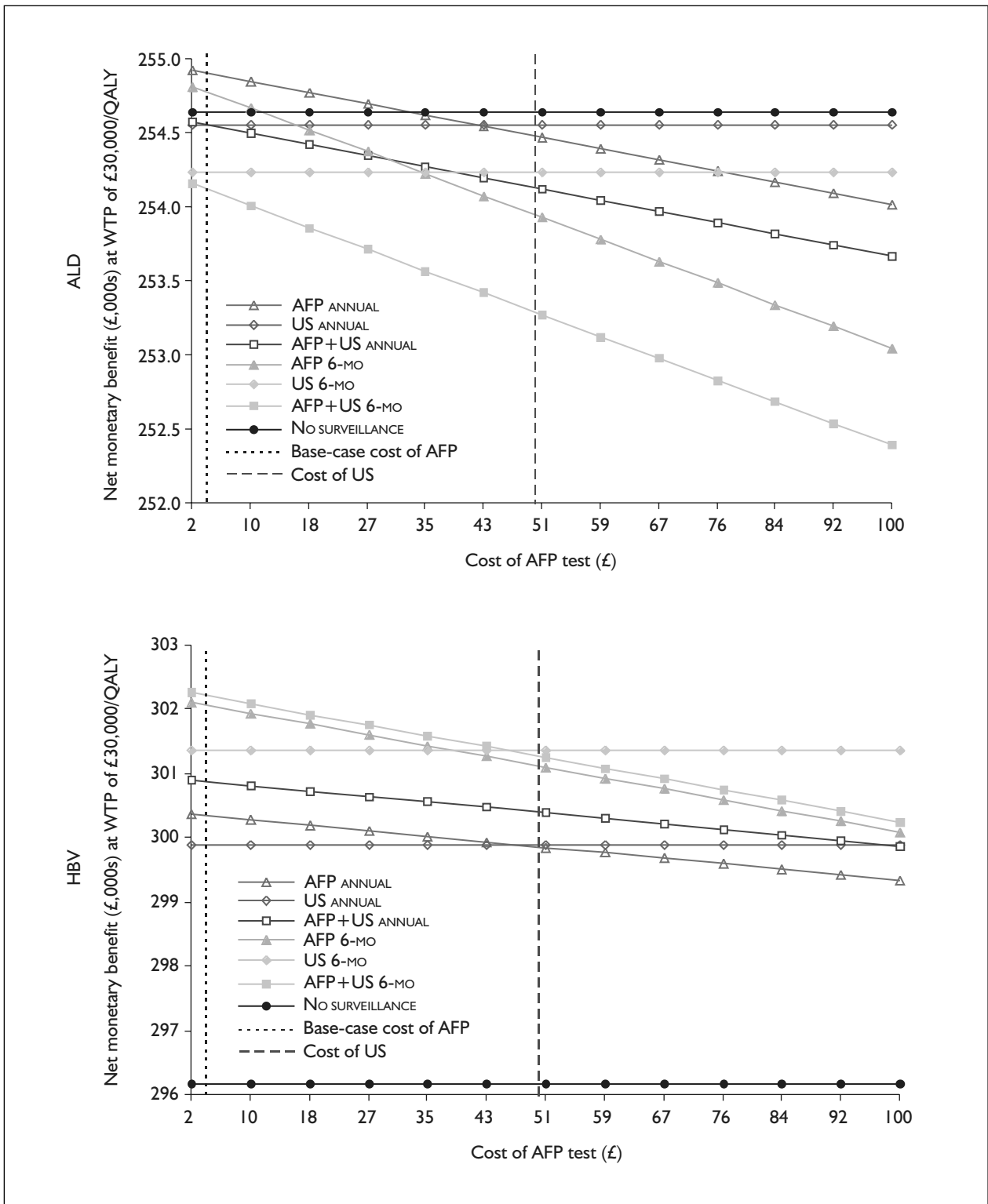


FIGURE 27 Detailed one-way sensitivity analyses: cost-effectiveness of surveillance relative to cost of AFP test (continued overleaf)

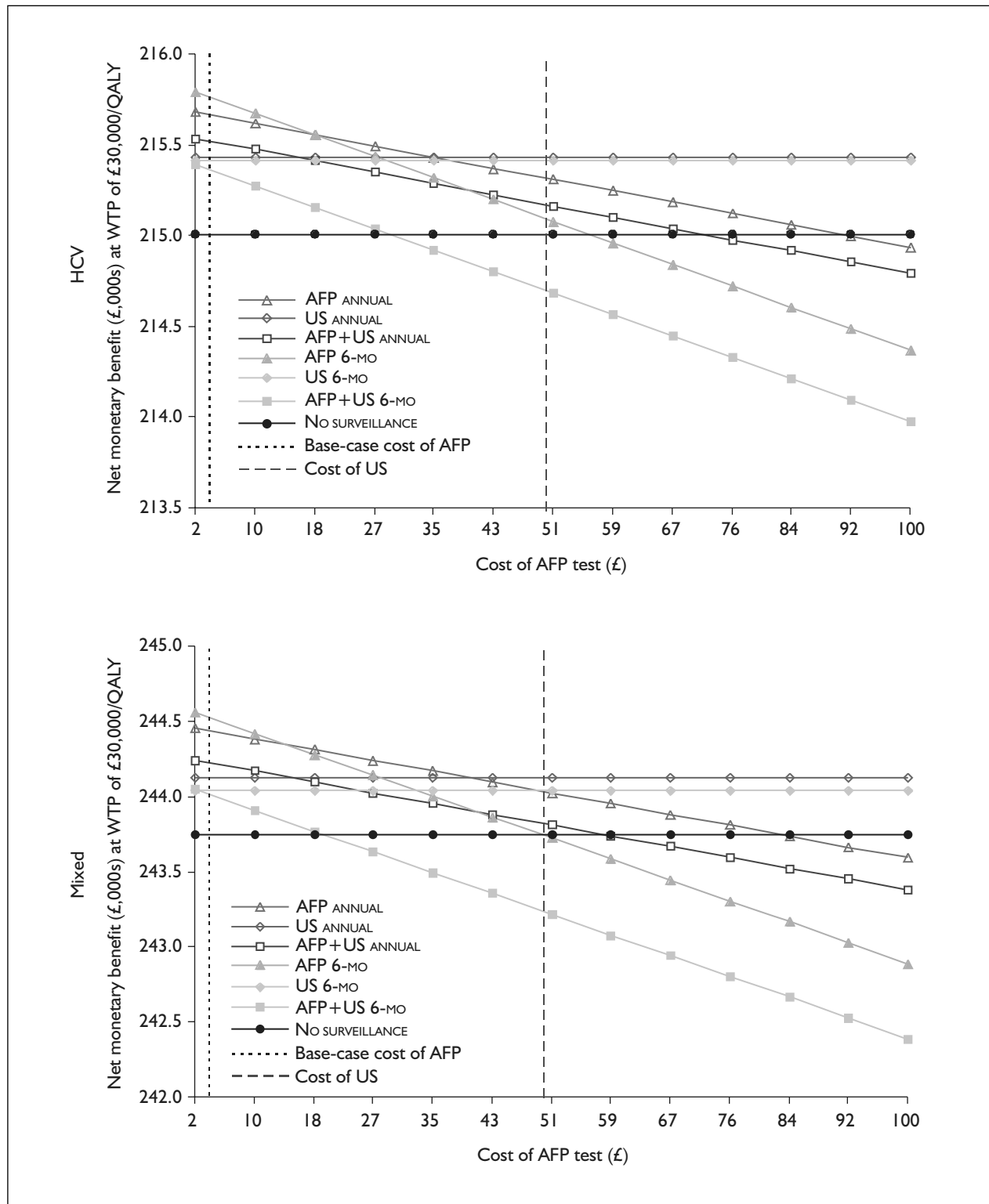


FIGURE 27 (continued) Detailed one-way sensitivity analyses: cost-effectiveness of surveillance relative to cost of AFP test

# Chapter 6

## Discussion

### Summary and interpretation of main findings

#### Effectiveness and other consequences of surveillance

Table 63 shows the effectiveness and other intermediate impacts of the six surveillance strategies and NO SURVEILLANCE in a mixed aetiology cohort (57.6% ALD; 7.3% HBV; 35.1% HCV). It should be noted that the model only included people with a diagnosis of compensated cirrhosis who are also eligible to enter a surveillance programme, based on age and the absence of pre-existing medical conditions that would preclude treatment with liver transplantation or resection (e.g. current alcohol or intravenous drug abuse).

The strategy of surveillance 6-MONTHLY AFP+US was the most effective strategy on all measures. Compared with NO SURVEILLANCE, this strategy is estimated to more than triple the number of people with operable HCCs at diagnosis, and almost halve the number of people who die from HCC. However, the cheapest surveillance strategy, ANNUAL AFP TRIAGE, still achieved substantial gains compared with NO SURVEILLANCE; for example, more than doubling the number of operable HCC tumours found, and increasing the number of small tumours found more than six-fold. On all effectiveness measures (except for the proportion of the cohort who have medium HCCs at diagnosis), surveillance with AFP TRIAGE

is as effective as or slightly more effective than surveillance with ultrasound at the same frequency.

#### Cost of surveillance

The undiscounted cost of the surveillance strategies varied from £40,300 per person for ANNUAL AFP TRIAGE to £42,900 per person for 6-MONTHLY AFP+US. Discounted (3.5%) costs ranged from £28,400 per person to £30,400 per person, respectively. Six-monthly surveillance is always more costly than annual surveillance, regardless of the test or tests used.

Only a small proportion (<4% of undiscounted costs) of these total costs result from the cost of the screening tests. However, screening test costs, and the cost of liver transplants and caring for people post-transplantation, accounted for most of the incremental cost differences between alternative surveillance strategies.

#### Cost-utility of surveillance

Both the deterministic results and the PSA strongly suggest that different surveillance strategies would be considered the most cost-effective in cohorts of different cirrhosis aetiology.

#### Cost-utility of surveillance in aetiology-specific cohorts

Table 64 details the strategies that, according to the base-case deterministic analysis, represent the optimal surveillance protocols in each aetiology-

**TABLE 63** Summary of results: effectiveness of surveillance

	NO SURV.	AFP ANNUAL	US ANNUAL	AFP+US ANNUAL	AFP 6-MO	US 6-MO	AFP+US 6-MO
% of cohort with operable HCCs at diagnosis	5.1%	11.9%	11.7%	13.5%	15.3%	15.0%	16.9%
% of cohort with small HCCs at diagnosis	0.3%	1.9%	1.5%	2.3%	3.1%	2.6%	3.7%
% of cohort with medium HCCs at diagnosis	2.1%	3.8%	4.1%	4.2%	4.2%	4.6%	4.4%
% of cohort getting OLTs	17.1%	19.1%	19.1%	19.2%	20.1%	20.0%	20.3%
% of OLTs which are for known HCC	8.3%	20.3%	20.0%	23.2%	25.3%	24.9%	27.9%
Proportion of cohort dying of HCC	19.9%	14.7%	14.9%	13.5%	12.0%	12.3%	10.8%
NNS to prevent one HCC death	–	19	20	15	13	13	11
Proportion of cohort dead by age 75	69.3%	68.4%	68.5%	68.2%	68.0%	68.0%	67.8%
NNS to prevent one premature death	–	114	117	93	78	79	68

**TABLE 64** Optimal decisions in aetiology-specific cohorts, based on deterministic incremental cost–utility results

Cohort	WTP threshold (£ per QALY)			
	Approx. 20,000	Approx. 30,000	Approx. 40,000	Approx. 50,000
ALD	NO SURVEILLANCE	ANNUAL AFP TRIAGE	6-MONTHLY AFP TRIAGE	6-MONTHLY AFP TRIAGE
HBV	6-MONTHLY AFP TRIAGE	6-MONTHLY AFP+US	6-MONTHLY AFP+US	6-MONTHLY AFP+US
HCV	NO SURVEILLANCE	6-MONTHLY AFP TRIAGE	6-MONTHLY AFP TRIAGE	6-MONTHLY AFP+US

**TABLE 65** Optimal decisions in aetiology-specific cohorts, based on probabilistic cost–utility results

Cohort	WTP threshold (£ per QALY)			
	Approx. 20,000	Approx. 30,000	Approx. 40,000	Approx. 50,000
ALD	NO SURVEILLANCE	NO SURVEILLANCE	6-MONTHLY AFP TRIAGE	6-MONTHLY AFP TRIAGE
HBV	6-MONTHLY AFP TRIAGE	6-MONTHLY AFP+US	6-MONTHLY AFP+US	6-MONTHLY AFP+US
HCV	NO SURVEILLANCE	6-MONTHLY AFP TRIAGE	6-MONTHLY AFP TRIAGE	6-MONTHLY AFP TRIAGE

specific cohort, with reference to hypothetical WTP thresholds of £20,000, £30,000, £40,000 and £50,000 per QALY.

Similarly, *Table 65* details the strategies which probabilistic analysis indicates are the optimal surveillance protocols in each aetiology-specific cohort, with reference to the same WTP thresholds.

The most noteworthy implication of these results is that, at any commonly adopted WTP threshold, the combined testing strategy of 6-MONTHLY AFP+US only appears cost-effective when used for those with HBV-related cirrhosis. Both deterministic and probabilistic analyses indicate that, for WTP thresholds approaching or exceeding the conventional UK level of £30,000 per QALY, 6-MONTHLY AFP+US is very likely to be the most cost-effective option in the HBV population.

For those with HCV-related cirrhosis, neither deterministic nor probabilistic analyses support the use of any surveillance strategy, unless WTP can be assumed to be £30,000 or higher. At this level, the optimally cost-effective strategy is 6-MONTHLY AFP TRIAGE. Deterministic analysis suggests that the most intensive surveillance policy, 6-MONTHLY AFP+US, is very close to achieving cost-effectiveness at a WTP of £50,000 per QALY in this population (ICER = £50,400 per QALY). However, when parameter uncertainty is considered in probabilistic analysis, results indicate that WTP would have to rise still further, to a level of around £65,000 per QALY, before 6-MONTHLY AFP+US becomes most likely to be optimally cost-effective.

Evidence is most equivocal in the cohort of individuals with ALD-related cirrhosis. No surveillance strategy appears favourable, on the basis of either deterministic or probabilistic analysis, at a WTP of £20,000. At an assumed UK WTP of £30,000 per QALY, deterministic analysis indicates that minimal surveillance with ANNUAL AFP TRIAGE should be cost-effective (ICER = £24,800 per QALY). However, the results of stochastic simulations suggest that NO SURVEILLANCE may remain the optimal strategy at this level, with ANNUAL AFP TRIAGE only becoming the strategy of choice if a slightly higher WTP (approximately £32,000 per QALY) is acceptable. It is only when WTP approaches £40,000 per QALY that the probability this strategy is optimally cost-effective exceeds 0.5. Both modes of analysis suggest that 6-MONTHLY AFP+US could only be considered cost-effective at very high levels of WTP (greater than £80,000 per QALY).

#### **Cost–utility of surveillance in mixed aetiology cohort**

Although we believe that the above is robust evidence, we recognise that the principle of adopting different surveillance regimens for patients with different aetiologies of cirrhosis may be considered unacceptable for practical reasons. Under these circumstances, the results of the pooled, ‘mixed aetiology’ cohort provide an indication of the most cost-effective policy that might be adopted across all three populations. *Table 66* details the optimal surveillance strategy in the mixed aetiology cohort, as indicated by deterministic and probabilistic analysis.

**TABLE 66** Optimal decisions in mixed aetiology cohort, based on deterministic and probabilistic cost–utility results

Cohort	WTP threshold (£ per QALY)			
	Approx. 20,000	Approx. 30,000	Approx. 40,000	Approx. 50,000
Deterministic	NO SURVEILLANCE	6-MONTHLY AFP TRIAGE	6-MONTHLY AFP TRIAGE	6-MONTHLY AFP TRIAGE
Probabilistic	NO SURVEILLANCE	6-MONTHLY AFP TRIAGE	6-MONTHLY AFP TRIAGE	6-MONTHLY AFP TRIAGE

The implications of these findings are fairly clear: surveillance of any kind can only be recommended if WTP exceeds £20,000 per QALY. If WTP is assumed to be £30,000 per QALY or higher, 6-MONTHLY AFP TRIAGE appears to be the most cost-effective surveillance protocol. From a cost-effectiveness perspective, this strategy remains the foremost option until WTP levels reach very high levels. The deterministic ICER for the next most effective strategy, 6-MONTHLY AFP+US, is £60,100. Similarly, probabilistic analysis suggests that WTP would have to approach £70,000 per QALY before 6-MONTHLY AFP+US could confidently be assumed to be more cost-effective than 6-MONTHLY AFP TRIAGE.

Taken in conjunction with the analysis of effectiveness summarised above, these findings are unambiguous. If one decision rule has to be applied across cirrhosis cohorts of all aetiologies, 6-MONTHLY AFP+US is always the most effective option and, at all plausible levels of WTP, 6-MONTHLY AFP TRIAGE is the most cost-effective strategy. The practical implication of this is that, in pure effectiveness terms, the optimal surveillance strategy in a mixed aetiology cohort would be to provide each patient with AFP assay and ultrasound imaging on a 6-monthly basis. However, when cost-effectiveness considerations are acknowledged, it is doubtful whether ultrasound should be routinely offered to those with blood-AFP of less than 20 ng/ml, unless policy makers are prepared to pay a very high price (>£60,000 per QALY) for each of the few additional cases this would detect.

## Interpretation of the results

### Usefulness of AFP

For all of the chosen measures of effectiveness and cost-effectiveness, both the deterministic and the probabilistic results point to AFP TRIAGE surveillance producing better outcomes than surveillance with ultrasound at the same frequency. Given that current guidelines do not recommend surveillance with AFP as the initial screening test,<sup>96</sup> this result requires further explanation and discussion.

This finding may be explained by a combination of factors:

- AFP tests appear to be substantially more effective than ultrasound at detecting small tumours. According to the evidence used in the model, 65% of tumours less than 2 cm in diameter secrete 20 ng/ml or more AFP. Recently published data suggest that this may be an overestimate, with the true proportion around 46%,<sup>329</sup> but this test is still markedly more sensitive than ultrasound, which will only detect 10.7% tumours less than 2 cm in diameter.<sup>256</sup> Published evidence suggests that, even for medium-sized tumours, AFP assay is more sensitive than ultrasound (62% and 28.6% of tumours detected, respectively).
- In the model, AFP-led surveillance strategies use AFP assay as a triage step, with all those with AFP of 20 ng/ml or above receiving ultrasound as the second diagnostic step. Therefore, the relatively high false-positive rate (of 9.4%) is largely corrected by the high specificity of ultrasound and CT and, according to the present screening algorithm, only around 1 per 1000 patients without HCC would be erroneously diagnosed.
- AFP is a very cheap test and, inevitably, this is a crucial consideration, from a cost-effectiveness perspective. Although the base-case parameter set may slightly overestimate the sensitivity of AFP, reanalysis with updated values did not affect the conclusion that, except in patients with HBV, 6-MONTHLY AFP TRIAGE (i.e. reserving ultrasound for those with AFP >20 ng/ml) is the optimally cost-effective approach. Moreover, the inexpensiveness of AFP means it may be possible to use it more frequently: in some cases (e.g. in the speculative scenario approximating the use of contrast-enhanced ultrasound), AFP-led surveillance was found to be cheaper than imaging at half the frequency (in turn, this enables it to be more effective at less cost).

Comparing the intermediate outputs for ultrasound-led and AFP TRIAGE strategies, the model predicts that a similar number of patients

with HCC will be identified and listed for transplantation but, when ultrasound-led surveillance is adopted, more patients are listed when their tumours are medium sized and a disproportionate number of these will subsequently be excluded from the list because their tumours grow to an extent that contraindicates OLT.

The fact that both the clinical guidelines currently applicable in the UK (Ryder, on behalf of the British Society of Gastroenterology)<sup>96</sup> and those recently published by the American Association for the Study Liver Diseases (AASLD)<sup>253</sup> dismiss the use of AFP testing as the initial screening test may reflect a number of things. These include the poor quality of evidence available (i.e. very little from well-designed non-experimental studies), in particular a lack of evidence concerning the relative performance of the two candidate screening tests as HCC tumours become progressively smaller (and thereby, more treatable). In addition, processes for clinical guideline development rarely give as explicit attention to cost and cost-effectiveness considerations as they do to clinical effectiveness.<sup>449</sup>

#### **AFP- or ultrasound-led surveillance policy**

A surveillance strategy that is led by either AFP or ultrasound runs the risk of serial false-negative findings. There is a proportion of tumours that never secrete AFP and will never be identified with the AFP TRIAGE approach. Equally, there is a proportion of potentially AFP-secreting tumours that will infiltrate diffusely and will remain undetectable by ultrasound. Guidelines recently issued by the AASLD suggest that combined strategies should be rejected and that ultrasound has the most favourable characteristics as a surveillance test. However, as described above, detection rates for AFP-led surveillance, despite the prevalence of non-secreting tumours, are more favourable for small tumours than ultrasound surveillance. This suggests that, if it is acceptable to tolerate the likelihood of serial false-negative results despite increasing tumour size in a minority of patients, an AFP-led strategy should be preferred over one led by ultrasound. Nevertheless, the precautionary principle might suggest that only a combined AFP and ultrasound strategy should be acceptable, to avoid serial false-negative results and the potential for patients to be fruitlessly subjected to inconvenient investigation with associated costs to health services. However, this study has shown that, across the whole population, such a strategy is unlikely to be considered cost-effective (at a WTP

of £30,000 per QALY). In turn, this may lead to a paradoxical rejection of all surveillance strategies, meaning that the considerable benefits of surveillance over no surveillance would be lost. The current study has not been able to model alternative, more complex strategies, in which both modes of investigation are included, such as intermittent ultrasound surveillance in AFP-negative cases as a 'rescue' measure for non-secreting tumours. This would increase the cost of surveillance programmes for an uncertain benefit and further work is necessary to understand the trade-offs that could be expected.

#### **Diagnosis versus surveillance test performance**

In the development and implementation of the model, we adopted the performance characteristics of tests as defined in diagnostic studies and applied these to simulate the likely performance of those tests in a surveillance programme. It has been argued that it is inadvisable to draw such inferences from one setting to another.<sup>253,276</sup> Such authors contend that the performance of a test as a surveillance tool can only be reliably discerned from surveillance studies.

We do not believe this argument applies in the case of the present model. Because the model relied on blinded diagnostic series which compare test findings against an optimal reference standard (explant pathology), it may safely be concluded that the results of such studies reflect the likely performance of each test in any individual instance.

In contrast, sensitivity and specificity estimates drawn from surveillance studies have two notable shortcomings, from the perspective of a modelling study. First, results are fundamentally tied to the frequency with which surveillance has been undertaken, and it is impossible to infer anything about the likely performance of the same test or combination of tests at a different frequency. Under these circumstances, it would be necessary to identify a separate parameter estimate for each strategy being modelled and assume no underlying heterogeneity in the populations under surveillance in each study. Of course, this would also rule out the simulation of speculative scenarios that do not represent recorded practice. Secondly, the sensitivity of screening tests is almost certainly exaggerated when derived from surveillance literature, as such series fail to account for the possibility that correctly identified lesions were missed in previous tests in the same patient. (In other words, a surveillance



programme counts each accurately identified HCC as a true positive, thereby masking the likelihood that such identifications may follow a series of false-negative tests in any individual case.)

### **Compliance**

In the evaluation of screening programmes, compliance with scheduled appointments and the means by which this is achieved are clearly important factors for consideration. Poor compliance with recommended screening policies can make the difference between an effective and cost-effective policy, and one which is neither effective nor cost-effective. The base-case analysis assumed 100% compliance with all scheduled appointments in an attempt to observe the characteristics of the surveillance strategies themselves without the added complications that reduced compliance might bring. The model did not include any measure of the administrative costs that might be associated with implementing such a programme, but assumed that on an individual basis these would be minimal.

To explore the effects of compliance on both the effectiveness and cost-effectiveness of surveillance, both a scenario analysis and a detailed one-way sensitivity analysis were performed. These reveal that higher levels of compliance, in terms of both a lower attrition rate from the programme and a higher proportion of appointments attended, result in a more effective surveillance programme (see the sections 'Scenario analyses', p. 80, and 'Detailed one-way sensitivity analyses', p. 89). As compliance is reduced, the cost-effectiveness of the strategies is improved, but this is at the considerable expense of effectiveness.

### **Tumour growth rate**

Unsurprisingly, in a model that distinguishes several classes of tumour size, and where medium-sized tumours are simultaneously much more detectable than small ones and yet still mostly amenable to treatment, tumour growth rates from small to medium and from medium to large appear to have a notable influence on cost-effectiveness in the one-way sensitivity analysis.

To investigate the impact of growth rates in greater detail, stratified scenario analyses were performed, simulating three mixtures of slow-growing and fast-growing tumours, instead of applying one average growth rate throughout the model. The results of these analyses were surprisingly unremarkable. The combination of

growth rates has an impact on the effectiveness and cost-effectiveness of surveillance (the more fast-growing the HCCs, the more cost-effective surveillance becomes). However, the incremental relationship between surveillance strategies is preserved, and the only practical implication of these extra findings is to suggest that, if the true mix of HCCs features a preponderance of slow-growing tumours, it may not be cost-effective to offer any sort of surveillance at a 6-monthly interval. Preliminary analyses were also performed using an alternative modelling approach, an individual sampling tumour growth model, in which individual differences in tumour growth rate were incorporated into the natural history of HCC. This model simulates individual patients with distinct characteristics, rather than a single, homogeneous cohort (further details of the methods used in developing this model can be found in Appendix 10). The preliminary outputs of this model confirm the provisional view that the Markov modelling approach may slightly underestimate the cost-effectiveness of surveillance.

### **Potential improvements in ultrasound test performance**

Ultrasound technology is a fast-moving area and improvement in the test performance of ultrasound imaging is expected in the near future. We attempted to explore this potential improvement in two ways. First, a scenario analysis was performed in which the costs and performance of ultrasound were increased in line with what one might expect from contrast-enhanced ultrasound techniques. Unfortunately, there is very little evidence available on which to base these assumptions and this analysis is therefore speculative. Secondly, a threshold analysis was performed in which the parameters characterising ultrasound test performance were varied over a range of correlated values according to tumour size. Cost considerations were overlooked in the threshold analysis in an attempt to clarify the relationships between test performance and effectiveness of the various surveillance strategies. It is worth noting that the test performance of the AFP test will never improve as long as the proportion of AFP-secreting and non-secreting tumours within the population of interest remains constant.

These additional analyses highlight several important issues. Increases in ultrasound test performance increase the effectiveness of all surveillance strategies. Ultrasound-led surveillance policies become more effective than the AFP TRIAGE policy when it can be assumed that

ultrasound is at least sensitive enough to detect one in five small tumours, one in three medium tumours and two in three large tumours. However, given the substantial difference in cost between AFP and ultrasound, it cannot be assumed that increases in ultrasound sensitivity will be possible at an acceptable cost; this is particularly evident in the ALD cohort. Indeed, the speculative scenario analysis using more sensitive but more expensive ultrasound suggests that it may be possible to detect more tumours at lower cost by increasing the frequency of a relatively inexpensive although insensitive test (e.g. AFP), rather than using a relatively expensive but more sensitive test (e.g. improved ultrasound) less often.

### **Surveillance by aetiology**

Using the best available data in the literature, the model was used to perform analyses for three cirrhosis aetiologies, ALD, HBV and HCV, and suggestions have been produced for the optimal surveillance strategy in terms of cost-effectiveness for each aetiology and for a mixed cohort derived from these patient groups. The optimal decision may differ for different aetiologies, with patients with HBV clearly benefiting from more intensive surveillance strategies at presumed levels of WTP. This may be due to the younger age at diagnosis of cirrhosis in this group. Successful treatment of HCC at a younger age results in greater long-term benefits in this patient group. It may therefore be valuable to assess the cost-effectiveness of surveillance among people diagnosed with HCV- and ALD-related cirrhosis at a younger age.

Although it may not be considered practical to offer different surveillance policies to different patient groups, it should be remembered that the summary results for the mixed cohort consider patients with ALD, HBV and HCV only, and are therefore not a true approximation of the mixed cohort of patients with cirrhosis in England and Wales. To improve the generalisability of the mixed cohort, one would need to consider the effectiveness and cost-effectiveness of surveillance for HCC in other groups with cirrhosis, such as people with haemochromatosis and primary biliary cirrhosis.

### **Frequency of testing**

In all of these analyses, the frequency of testing appears to be more important than the choice or number of tests used. One corollary of this is that surveillance at more frequent intervals than every 6 months may well be worthy of consideration. In much the same way that 6-MONTHLY AFP TRIAGE proves more cost-effective than ANNUAL AFP+US, it is quite possible that a quarterly AFP-led

strategy, for instance, may prove to be superior to 6-MONTHLY AFP+US.

This was explored further using an individual sampling tumour growth model approach, which is able to investigate surveillance frequency as a variable. *Figure 28* shows the effects on costs and benefits of increasing the frequency of screening from once per year to 12 times per year. For comparison, a non-surveillance situation is also shown. The graphs confirm results obtained from the Markov model in that screening at a frequency of once and twice per year would both be considered cost-effective at the £30,000 per QALY level. However, particularly in the HBV cohort, testing conducted at considerably more frequent intervals would also be considered cost-effective. These results highlight the need for further research into the optimum surveillance strategy in each disease aetiology, as it may not be confined within the conventional strategies to which the comparisons in this project are limited.

### **Discounting**

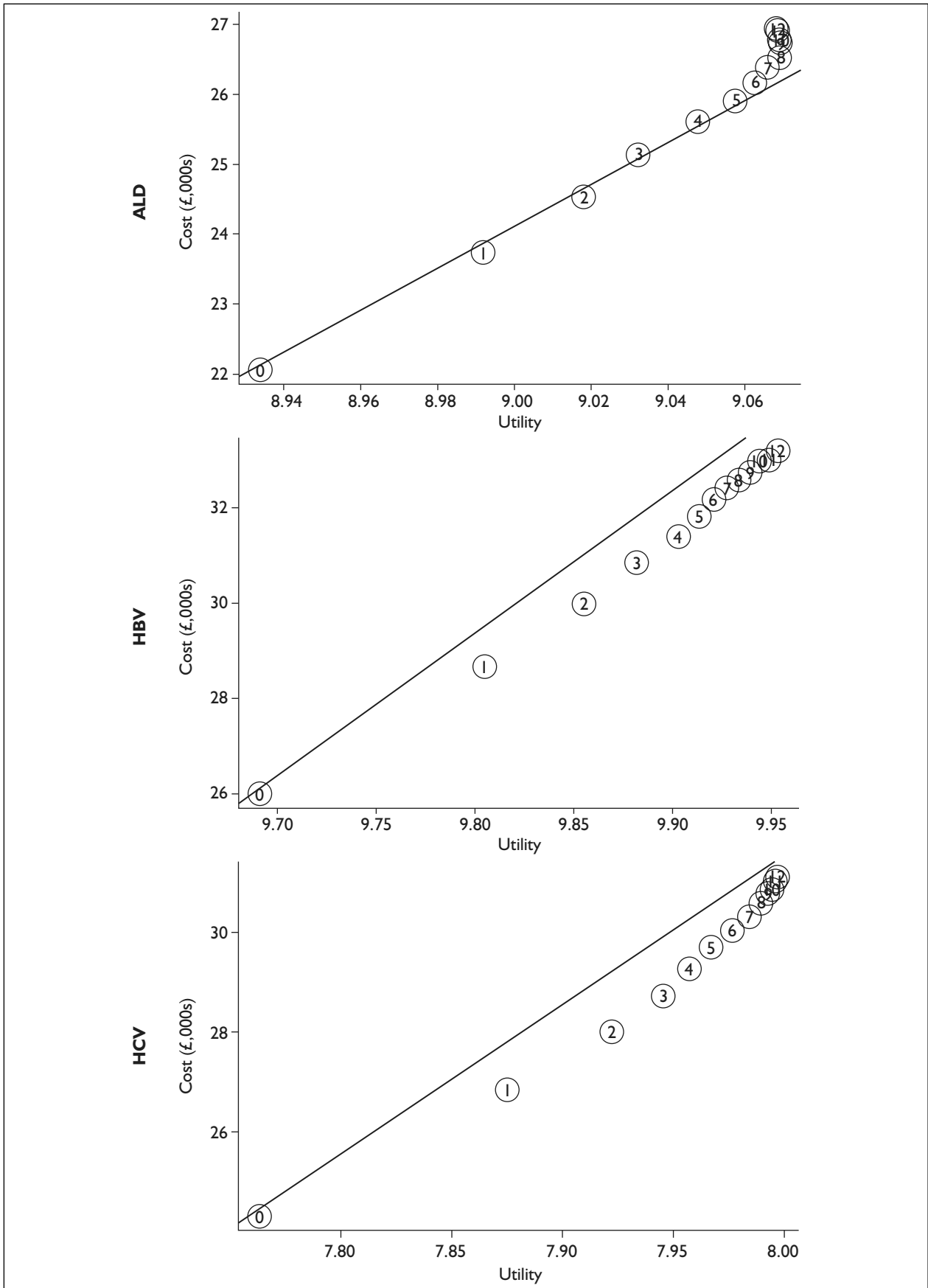
The results from the model are extremely sensitive to the level of discounting applied to costs and benefits (see the section 'Sensitivity to discount rate', p. 74). The undiscounted base-case ICER for the comparison of NO SURVEILLANCE with 6-MONTHLY AFP+US is £19,400 per QALY. This increases to £27,900 per QALY using the currently recommended discount rate of 3.5% for costs and benefits. Using the previously recommended discount rates of 6% for costs and 1.5% for benefits would have produced markedly different results, reducing this ICER to £16,400 per QALY.

## **Strengths and weaknesses of the study**

### **Strengths of the evaluation**

This is the first analysis of the effectiveness and cost-effectiveness of surveillance of cirrhosis for HCC that has been conducted to inform policy in the UK NHS setting. Comprehensive literature searches were conducted to inform the model parameters, wherever possible choosing data either derived from the UK population or most likely to be applicable to a UK population.

The analyses include the consideration of a mixed aetiology cohort and three individual cirrhosis aetiologies (ALD, HBV and HCV) which comprise the majority of patients currently diagnosed with cirrhosis in the UK, extensive analysis of the



**FIGURE 28** Cost–utility of surveillance in aetiology-specific cohorts as estimated by individual sampling tumour growth model. Numbers show frequency of screening (tests per annum); the diagonal line represents the ICER of £30,000 per QALY relative to no surveillance.

uncertainty of the model with one-way and probabilistic sensitivity analysis and a preliminary value of information analysis, and several scenario analyses to explore the impact of different levels of compliance with the programme, variations in tumour growth rate and the implications of enhanced imaging performance attributed to emerging technologies (contrast-enhanced ultrasound).

Extensive exploration of possible model structures has allowed careful consideration of the clinical situation. In particular, we believe that the following aspects of the model more appropriately capture the disease and surveillance process and impacts than previously published models in this field:

- **Heterogeneity in aetiology of cirrhosis:** the study has accounted for the substantial differences in age-related incidence, natural history and response to treatment that exist according to cirrhosis aetiology. As a result, the model is able to demonstrate that different approaches to surveillance may be justified according to different causes of cirrhosis.
- **Tumour size:** Three tumour sizes (<2, 2–5 and >5 cm) have been defined and modelled. Although this is not the first modelling analysis to simulate tumours of different size (e.g. see Arguedas and colleagues<sup>304</sup> and Patel and colleagues<sup>307</sup>), we believe that this is the first to simulate the likely impact of different tumour sizes on screening test performance, the likelihood of symptomatic/incidental diagnosis and the treatability of detected HCC tumours by either liver resection or transplantation.
- **Surveillance protocols:** the study has separately estimated the performance of various combinations of tests according to testing protocols believed to be used in the UK at the present time.
- **Symptomatic or incidental detection of HCC:** to capture the effects of a surveillance programme on the detection of HCC tumours within a given cohort appropriately, the model also allowed people to present with an HCC tumour outside the surveillance programme as a result of either symptomatic or incidental diagnosis. The rate at which this occurs is based on the best available evidence in the literature.
- **Treatment of HCC to reflect a mixture liver transplantation or resection:** since both liver transplantation and liver resection are currently the main surgical treatment options for newly diagnosed HCC tumours, the costs and long-term effectiveness of both have been modelled. This is particularly important because liver

transplantation is substantially more expensive than liver resection, and one of the intended impacts of surveillance is to detect HCC tumours earlier (and therefore when they are smaller, and more amenable to treatments other than liver transplantation).

### Limitations of the assessment

Model-based cost-effectiveness analyses are an inevitable consequence of the need to integrate data and assumptions about a wide variety of factors relating to the natural history of a disease process, the performance of screening and diagnostic tests, the care and treatment pathways for different diagnosed disease states, and the resultant life expectancy and quality of life of being in different disease states or having different treatments.<sup>450</sup> There is always a balance to be struck between reflecting as many of the critical relationships and factors that impinge on a decision as possible, and keeping the model sufficiently simple and comprehensible that its results are believed. In addition, the degree of sophistication of any decision model is always constrained by the availability of valid and reliable research evidence to inform the parameter values in order to ‘work’.<sup>451</sup>

There is very little published evidence available on which to base many of the parameter estimates for the model directly, and virtually none originates in the UK. Some parameters, such as the rates of symptomatic/incidental diagnosis of different sized tumours, were estimated indirectly through calibrating the model results against other data sources. Other estimates, such as those surrounding the natural history of HCC in HCV, have not been well characterised.

As the primary focus of this evaluation is the effectiveness and cost-effectiveness of surveillance of patients with cirrhosis for HCC, a simplified approach to modelling treatment was used, in which transplantation and liver resection are the only curative treatment options available. A small proportion of ‘small’ and ‘medium’ tumours and all ‘large’ tumours are deemed to be surgically untreatable. The costs of some palliative therapies for a proportion of people with surgically untreatable tumours were included, but any benefits attributed to these were only crudely incorporated (an assumed reduction in mortality rate).

Ablative therapies are available to patients in the UK both as well as and instead of transplantation and resection. Theoretically, ablative therapies administered to people on the waiting list serve to

slow down the disease process and result in fewer people becoming ineligible for treatment before a liver becomes available. However, unambiguous evidence about the effectiveness of this approach is still lacking. It remains possible that such therapies have little consequence for overall prognosis.<sup>452</sup>

It may be a limitation that the parameters of the model do not capture the effect of cirrhosis aetiology on AFP levels. In the model, AFP assays have the same sensitivity and specificity across all aetiologies. As discussed in the section 'Test performance', p. 41, this assumption may not be accurate. In particular, some evidence suggests that HCCs developing in posthepatic cirrhosis are more likely to secrete significant levels of AFP than those that arise in livers with ALD-related cirrhosis. Similarly, raised AFP for reasons other than HCC development may be more common in those with HBV- and HCV-related cirrhosis. However, because the evidence base on these questions is insufficiently robust to support aetiology-specific estimates, the same AFP levels were applied to all three cirrhosis aetiologies.

Entry to the surveillance programme assumes that high-risk activity (e.g. alcohol abuse or injecting drug use) has discontinued, but this may not be a realistic assumption. The impact of this assumption being too optimistic could be three-fold. First, large numbers of people within the mixed or ALD cohorts who continued to abuse alcohol would result in unnecessary expenditure on surveillance producing no benefits, if identified patients were then ineligible for available treatment options. Secondly, continued alcohol abuse would lead to increased rates of decompensation not captured by the model. Thirdly, no excess risk of mortality associated with compensated cirrhosis has been modelled; this may be too conservative in patients with past/current high-risk behaviour. For all of these reasons, this assumption would tend to bias the model in favour of surveillance in this patient group.

For simplicity, the model assumes that the various aetiologies of cirrhosis are mutually exclusive. In reality, many people develop cirrhosis following exposure to more than one risk factor. The present findings are unable to account for the likely effectiveness and cost-effectiveness of surveillance in individuals who are, for example, seropositive for both HBV and HCV, or those whose HCV coexists with a history of excessive alcohol consumption. However, if such subgroups could be

accurately identified and appropriate data made available, the model could easily be used to simulate and evaluate the various surveillance strategies in these populations.

In terms of uncertainty to do with the model's structure, the simplifying assumption was made that moving from compensated to decompensated cirrhosis is irreversible. While this may be a reasonable assumption for those with HCV-related or alcohol-related cirrhosis, it may not be the case for HBV-related cirrhosis, where some newer treatments show evidence of the reversibility of decompensated cirrhosis. Therefore, the estimates of HBV-related disease progression without surveillance may be too high. It was also assumed that there is no excess mortality associated with compensated liver cirrhosis, which differs from two previously published cost-effectiveness analyses.<sup>306,307</sup>

Costing was conducted using a pragmatic costing approach from an NHS perspective. In adopting an NHS perspective we acknowledge that this ignores some costs to patients and their families that would inevitably follow from taking part in the surveillance programme. There is no research to indicate how large these costs might be.

The Markov approach to modelling assumes 'no memory' from previous states. This means that, for example, the probability of moving from one disease state to another is dependent only upon the disease state that people are already in, and not on how long they have been in that state. This lack of memory may be important for analysing this disease process and decision problem in three main areas:

- In contrast with one of the other published modelling studies,<sup>306</sup> it was assumed that the incidence of HCC is independent of how long people have been living with the compensated or decompensated cirrhosis.
- No relationship was assumed between the rate of progression from small to medium-sized HCC tumours, and that from medium-sized to large tumours (although it is believed that tumours that are fast- or slow-growing when they are small are likely to remain so as they get bigger). The implications of this modelling limitation were explored in a scenario analysis with stratified tumour growth rates.
- It was also assumed that the performance of follow-up diagnostic tests is unaffected by knowledge of the result of the initial screening test. For example, it is plausible that, following

an AFP result of >400 ng/ml, radiologists may look harder to find a possible HCC than when following a lower AFP result. However, in the absence of any reliable quantitative evidence concerning how initial screening test results may alter the sensitivity or specificity of subsequent tests, the performance of tests was kept the same throughout the model regardless of their position in the testing sequence.

Another possible departure from clinical reality is the model's reliance upon absolute thresholds for serum AFP being exceeded at particular time-points. Not only may clinicians alter their diagnostic follow-up according to a larger number of notional AFP thresholds, but follow-up may differ according to a patient's pattern of change in AFP levels (thus, low absolute but consistently increasing AFP levels may arouse clinical suspicion that a tumour is present). For modelling simplicity, and lacking reliable evidence on this possibility, we chose not to model such changes over time.

Finally, as stated in Chapter 3, owing to limitations of computational capacity and time, no value of perfect information analyses was performed in relation to particular parameters (or groups of related parameters). Were these resources available, a partial EVPI analysis would enable some notional upper bounds to be placed on the potential monetary value of research designed to increase the precision of these parameters. These EVPI estimates would therefore represent absolute upper limits on the amount that society should

spend on any planned study (e.g. a trial or an observational study) to estimate them. However, it should also be noted that an important limitation on any further value of information analysis is the substantial uncertainty surrounding the number of people in the UK with a confirmed diagnosis of cirrhosis.

## Comparison with other studies

As described in Chapter 1, three comparable cost-effectiveness analyses were identified in the literature.<sup>304,306,307</sup> Appendix 11 illustrates some of the key differences in model assumptions between the present model (HCV cohort) and these previously published analyses. Although each of the models has its own strengths and weaknesses, we believe that the present model is more realistic in capturing some of the most critical assumptions that research evidence and logic suggest will impact on the cost and effectiveness of surveillance. The results of the cost-effectiveness analyses are summarised in *Table 67*.

## Implications for policy

The results show that surveillance strategies for HCC are effective, and can often be considered cost-effective in patients with cirrhosis. We believe that the implementation of formal surveillance programmes should be considered where they do not currently exist.

**TABLE 67** Comparison of present study with other published cost-effectiveness analyses: results

	PenTAG	Arguedas <sup>304</sup>	Lin <sup>306</sup>	Patel <sup>307</sup>
<b>Costs</b>				
No surveillance	£27,600	(\$190,655) <sup>a</sup> £152,400 <sup>d</sup>	(\$46,232) <sup>b</sup> £32,000 <sup>d</sup>	(\$53,200) <sup>a</sup> £42,500 <sup>d</sup>
6-monthly AFP+US	£31,900	(\$196,660) <sup>a,c</sup> £157,200 <sup>d</sup>	(\$57,168) <sup>a</sup> £39,500 <sup>d</sup>	(\$173,500) <sup>a</sup> £138,700 <sup>d</sup>
Annual AFP+US	£30,400	NA	(\$53,145) £36,700 <sup>d</sup>	NA
<b>QALYs</b>				
No surveillance	8.087	5.268	6.269	14.754
6-monthly AFP+US	8.238	5.493	6.650	15.243
Annual AFP+US	8.197	NA	6.569	NA
NA, not applicable.				
<sup>a</sup> In 2000 US dollars discounted at 3% per year.				
<sup>b</sup> In 2003 US dollars discounted at 3% per year.				
<sup>c</sup> 6-monthly screening, but alternating the AFP and US test.				
<sup>d</sup> Inflated and translated from US dollars to 2005 pounds sterling.				

The results also suggest that different surveillance strategies in patient groups with different underlying causes of cirrhosis may provide the best value for money, if appropriate recall systems could be implemented, and also if this was judged to be ethically acceptable.

A surveillance strategy in which AFP testing is used as a triage step probably represents the best value for money.

These results also suggest a possible shift in the clinical settings where cirrhosis surveillance is conducted; as AFP triage appears to be a highly cost-effective strategy, either annually or 6-monthly, it may be more appropriate to perform the initial screening test in the primary care setting.

If effective surveillance programmes were to become widespread across the UK against a background of limited organ supply, the waiting list for liver transplants would undoubtedly increase. Detailed exploration of this was beyond the scope of this project, but preliminary findings suggest that this may be an important issue.

## Recommendations for further research

### Model development

- Extensive value of information analysis should be used to identify which parameters or groups of parameters contribute most to the uncertainty in the cost–utility results, and therefore suggest priorities for further primary research.
- Alternative modelling methods should be used to account for heterogeneity in the patient population, so that the impact of factors such as tumour growth rate, tumour characteristics and the variability in individual patients' serial test results may be accurately assessed. Such methods could also be used to investigate the optimal surveillance strategy, optimal surveillance interval and the effects of surveillance on waiting lists for liver transplantation.
- Further investigation is needed into the accepted cut-off levels for AFP tests and how different cut-off levels impact on the effectiveness and cost-effectiveness of surveillance for HCC.

- Further modelling studies should investigate innovative surveillance strategies not currently undertaken in clinical practice.
- Further modelling studies are needed to investigate the impact of alternative treatment modalities, (e.g. more resection of small tumours, radiofrequency ablation as a 'curative' treatment of small tumours), because identifying more operable HCC tumours will probably lead to longer transplant waiting lists.
- Further modelling is needed of the impact of age at diagnosis of cirrhosis on the cost-effectiveness of surveillance strategies.
- Anecdotal reports suggest that non-alcoholic fatty liver disease is increasing in incidence and will soon represent the second largest cause of cirrhosis in the UK. Further modelling studies are needed to assess the effectiveness and cost-effectiveness of surveillance in this patient group.

### Other research

- The effectiveness and cost-effectiveness of microbubble ultrasound technology to detect HCC tumours should be investigated, and the test performance in various stages of cirrhosis/aetiologies compared with explant pathology.
- Epidemiological research in the UK is needed to assess the incidence and rate of tumour growth of HCC in different cirrhosis aetiologies.
- The association between the level of AFP secreted and tumour size in different cirrhosis aetiologies needs to be assessed.
- Detailed observational research is needed on the epidemiology and natural history of ALD-related cirrhosis. Despite existing evidence that ALD accounts for the majority of the UK's disease burden of cirrhosis, and emerging evidence that alcohol consumption is rising, ALD-related cirrhosis remains particularly poorly described in the literature.
- Observational studies could be conducted which collect AFP measurements on the same population of people with cirrhosis over time, and investigate the relationship between the emergence or presence of HCC tumours and patterns of change in AFP levels over time (as opposed to the predictive ability of particular absolute AFP thresholds).
- Quality of life studies should assess the utility of all stages of disease, during assessment for treatment, during and post-treatment in all cirrhosis aetiologies in a UK population.







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### Contribution of authors

Dr Jo Thompson Coon (Research Fellow) was project manager and contributed to model design,

identification of inputs for model, interpretation of results and report preparation. Dr Rob Anderson (Senior Lecturer in Health Economics) gave project direction and contributed to model design, economic evaluation and interpretation of results and report preparation. Mr Gabriel Rogers (Research Assistant) supported the project by carrying out the systematic review and searches for parameter estimates, and contributed to model design, identification of inputs for the model, analysis and interpretation of results and report preparation. Dr Matthew Cramp (Senior Lecturer in Hepatology) gave clinical advice and contributed to model design and interpretation of results. Dr Simon Jackson (Consultant Gastrointestinal Radiologist) gave clinical advice and contributed to model design and interpretation of results. Dr Steve Ryder (Senior Lecturer in Hepatology) gave clinical advice. Mr Paul Hewson (Senior Lecturer in Statistics) developed and executed the Markov model and contributed to the analysis and interpretation of results. Dr Dave Wright (Reader in Applied Medical Statistics) contributed to the development and execution of the Markov model, developed and executed the individual patient model, and contributed to the analysis and interpretation of results. Ms Alison Price (Information Scientist) provided the literature search and retrieval. Dr Ken Stein (Senior Lecturer in Public Health) contributed to the study design and report preparation and gave methodological advice.





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# Appendix I

## Assessment protocol

### Project title

Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.

### Planned investigation

#### Research aim and objectives

##### Aim

To evaluate the effectiveness, cost-effectiveness and cost-utility of surveillance of patients with cirrhosis, using periodic serum alpha-fetoprotein testing (AFP) and/or liver ultrasound examination (LUS) to detect hepatocellular carcinoma (HCC), followed by treatment with liver transplantation or resection, where appropriate.

##### Objectives

1. Carry out a systematic review of randomised controlled studies examining the effectiveness or cost-effectiveness of surveillance of cirrhosis for HCC.
2. Construct a decision-analytic model to estimate the cost-effectiveness and cost-utility (cost per QALY) of surveillance by synthesising available evidence on: sensitivity and specificity of AFP and LUS; natural history of cirrhosis; outcomes of transplantation and resection; acceptability of surveillance; quality of life and costs.

The model will allow the following comparisons to be made:

- (a) surveillance using combined AFP/LUS (current guidelines) versus no surveillance and versus surveillance using AFP or LUS alone
- (b) surveillance annually versus surveillance every 6 months using AFP or LUS or AFP+LUS.

#### Existing research

HCC is the fifth most common cause of cancer globally and incidence is rising, mainly as a consequence of epidemics of hepatitis B virus (HBV) and hepatitis C virus (HCV).<sup>73</sup> Cirrhosis is the most important risk factor for development of HCC, although risk of HCC varies according to the underlying cause of liver disease. Risk appears to be higher in patients with HBV surface antigen

(HBsAg) than in patients with HCV.<sup>67</sup> Cirrhosis from either HCV or HBV carries a high risk of HCC, of around 3–5% per annum,<sup>25</sup> although estimates above and below this range have been reported.<sup>67</sup> HCC developing in the absence of cirrhosis is unusual: it may be seen in HBV disease, but is rare in chronic HCV disease.<sup>453</sup> Incidence of HCC in people with alcoholic liver disease is similar to viral hepatitis, although survival is strongly affected by other consequences of alcohol misuse, such as cardiovascular disease.<sup>96</sup>

Surveillance programmes are common, although variation exists in approaches taken<sup>96</sup> and direct evidence on the effectiveness and cost-effectiveness of surveillance is scarce.<sup>454</sup>

The British Society for Gastroenterology recommends screening using AFP and LUS at 6-monthly intervals, based on estimates of tumour doubling times.<sup>96</sup> AFP and LUS are thought to identify tumours of smaller size than would present in the absence of surveillance. This may lead to improved survival.<sup>96</sup> Neither AFP nor LUS is ideal for detecting HCC. Some tumours do not produce AFP, leading to false negatives. False-positive results may arise from nodule regeneration in viral hepatitis. Ultrasound, which is operator dependent, is sensitive and specific for large tumours, but sensitivity is low in small lesions (less than 2 cm diameter). Although surgical resection and tumour ablation (using a variety of techniques) are available, liver transplantation remains the treatment of choice in HCC. Recurrence is rare after transplantation in patients with small tumours and prognosis returns to that of the underlying liver disease.<sup>455</sup> Resection, which is suitable only for people with good liver function owing to the risk of postoperative hepatic decompensation, has similar short-term effectiveness to transplant (up to 3 years), but longer term tumour-free survival is worse.<sup>96</sup>

A Cochrane review, published in 2003 and based on searches carried out in 2000, identified two randomised trials of AFP and LUS for surveillance of people with chronic HBV disease.<sup>456</sup> However, in one study the proportion of people with cirrhosis is not reported. Only 4% were cirrhotic in

the other study. Initial searches have revealed no RCTs of surveillance programmes in people with cirrhosis. Modelling studies are therefore an appropriate next step in the development of a robust evidence base for this intervention.

Preliminary searches have identified one Markov modelling study of the cost-effectiveness of surveillance.<sup>307</sup> Although published recently, this was carried out in the USA and is therefore unlikely to be directly relevant to the UK healthcare system.

### Research methods

The project will have two elements. In the first, an exhaustive and systematic review will be carried out to identify and, where possible, synthesise the results of existing research into the effectiveness or cost-effectiveness of surveillance of cirrhosis for the development of HCC.

The second, and probably more fruitful approach, will be the development of a decision-analytic model to estimate the effectiveness and cost-effectiveness of surveillance.

Details of the methods to be used in these two aspects of the assessment are given in the following sections.

### Systematic review

The systematic review will use a similar approach to the Cochrane review published in 2002,<sup>456</sup> but the population of interest will be limited to people with cirrhosis. Although the commissioning brief suggests that no RCTs have been performed to address the research question, there is no evidence that this conclusion has been reached by a systematic review. We therefore propose carrying out a range of searches to confirm this finding.

### Search sources

The following public electronic sources will be searched by a specialist information scientist:

- MEDLINE
- Embase
- Cochrane Controlled Trials Register
- BIOSIS
- DARE
- ISTP (Index to Scientific and Technical Proceedings)
- ISI Science Citation Index
- National Research Register.

In addition, the coordinating editor of the Cochrane Hepato-Biliary Group (Professor

Christian Gluud) has agreed to carry out searches on the Review Group's Controlled Trials Register.

Search terms used across all sources will include the following (with, where appropriate, truncation and use of wildcards): "cirrhosis"; "carcinoma, hepatocellular"; "hepatoma"; "alpha fetoprotein"; "ultrasonography AND liver"; "ultrasound AND liver"; "mass screening"; "sensitivity AND specificity". Searches will be carried out with and without the use of thesaurus terms. Reference Manager software will be used to manage duplicate citations.

### Inclusion criteria

Two reviewers will consider the outputs of searches against inclusion criteria with resolution of disagreement by recourse to a third reviewer where necessary.

Inclusion criteria will include:

- randomised controlled trials
- publication in English
- study population (total or separately reported) with cirrhosis of known underlying cause (HCV, HBV or alcohol)
- surveillance using AFP or LUS (separately or in combination) compared to no intervention or to either AFP or LUS alone with findings reported according to underlying cause of cirrhosis (HCV, HBV or alcohol).

Outcomes will include:

- overall mortality
- mortality from HCC
- number of cases of HCC detected
- number of cases of 'small' HCC detected (less than 3 cm diameter)
- number of surgically resected HCCs
- survival times
- technical performance of AFP and LUS (sensitivity, specificity, and positive and negative predictive value).

Data will be extracted by one reviewer and checked by a second. Methodological quality of RCTs will be assessed using the criteria reported in the CRD Report No. 4:<sup>321</sup>

- randomisation sequence generation
- concealment of allocation sequence
- similarity of groups at baseline
- eligibility criteria specified
- blinding of assessors
- blinding of care provider



- blinding of participants
- cointervention
- loss to follow-up
- appropriateness of statistical methods
- intention-to-treat analysis.

### Synthesis

Trial results will be tabulated and described. If sufficient studies are identified, publication bias will be explored using a funnel plot.

Heterogeneity will be explored visually using a forest plot and by careful consideration of differences in the study populations and interventions used. If possible, meta-analysis will be carried out, using a random effects model. Heterogeneity will be assessed statistically using the  $I^2$  statistic and  $\chi^2$  test for homogeneity.

### Decision analytic model

#### Model structure

The model will be developed in collaboration with two clinical academic hepatologists (Dr Matthew Cramp and Dr Steve Ryder, author of the British Society for Gastroenterology guidelines on diagnosis and treatment of HCC) and a gastrointestinal radiologist (Dr Simon Jackson). The technical performance of the surveillance tests will be modelled using simple decision trees. Inference will be made using a Markov chain Monte Carlo (MCMC) simulation approach. Consequences of cirrhosis will include: decompensation (which will be modelled as a single state, encapsulating ascites, encephalopathy and variceal haemorrhage), HCC and death.

Broadly, there are three treatment options for HCC (identified through surveillance or as a result of spontaneous presentation): liver transplantation, resection or, in some cases, ablation techniques. In the short term, resection and transplantation have similar efficacy, but in the longer term transplantation is associated with improved survival and is therefore the treatment of choice. However, the supply of donor organs remains limited and therefore a mixture of resection and transplantation is currently undertaken in the UK. We will model this mixed approach to treatment (i.e. transplantation and resection) in the base case by using summary estimates of the effectiveness and adverse events for each treatment approach and combining these using an estimate of the distribution of use for each. This may be difficult to obtain from published literature, in which case a limited search of the grey literature will be carried out through contact with clinical experts, seeking audit data. If

no data are available on the distribution of treatment approaches, this will be estimated from expert opinion.

Three study populations will be modelled, according to the underlying cause of cirrhosis (HCV, HBV and alcohol). If sufficient information is available, the impact on risk of progression of other factors such as gender, age and severity of cirrhosis may be included. We will not consider cases of coinfection with HBV+HCV or with hepatitis+HIV.

As well as cause-specific mortality, 'background' mortality from all causes will be included. In the case of alcoholic cirrhosis, specific estimates for mortality from non-hepatic disease will be sought. For viral hepatitis, background mortality will be modelled on the basis of general population estimates.

The model will run for the lifetime of the populations.

#### Comparisons

The decision-analytic model will facilitate the following comparisons:

1. surveillance using combined AFP/LUS (current guidelines) versus no surveillance and versus surveillance using AFP or LUS alone
2. Surveillance annually versus surveillance every 6 months using AFP or LUS or AFP+LUS

#### Obtaining inputs

The commissioning brief states that:

Secondary research is required in the form of a systematic review of the elements contributing to the effectiveness and cost-effectiveness of surveillance for hepatocellular carcinoma (HCC) including the effectiveness of early treatment.

This requires clarification on two counts. First, a range of reviews, and not a single review, would be required. Secondly, it is not clear how the term 'systematic review' should be interpreted in this context. There are concerns among researchers carrying out modelling studies, that if a requirement for demonstrable exhaustiveness in the identification of potential values for model parameters is imposed this will (a) greatly increase the work involved in developing an appropriate model, and (b) be inefficient because exhaustive pursuit of possible values for parameters which are not important to the decision model would add nothing to the evaluation but increase costs of production.

The HTA programme defines systematic review as follows: “Reviews ... are termed ‘systematic’ when the account of the search, appraisal and synthesis methods would, in theory, permit the replication of the review by others”.

We interpret this as meaning that transparency is the critical feature of ‘systematicity’ in this context which will therefore be applied to the identification and incorporation of inputs for the economic model of surveillance of cirrhosis.

Model parameter estimates and accompanying measures of precision will be retrieved from published or unpublished literature wherever possible. Relevant papers will be identified by searching electronic resources (listed above), inspecting reference lists from retrieved articles and contact with clinical experts.

Each search will be specified as the project develops. Where possible, the intensity of literature searches will be informed by the importance of model parameters to uncertainty in the outputs (cost-effectiveness and cost-utility). For each parameter in the model, separate research questions will be specified, potential inputs identified and the choice of parameter values made explicit.

The main areas for which values will be required in implementing the model will be:

- technical performance of AFP and LUS in people with cirrhosis and HCC
- progression from compensated cirrhosis to decompensation, HCC or death
- spontaneous presentation with HCC
- effectiveness and harms of liver transplantation and tumour resection for HCC
- mortality from HCC
- compliance with surveillance
- costs
- quality of life (utility) associated with cirrhosis, HCC and being under surveillance.

Studies will be selected on the basis of methodological quality and relevance to the overall research question. For example, for progression of cirrhosis, the best studies will be recent, large, cohorts, measuring progression to decompensation, HCC and death. International studies are more likely to have greater power, and are probably relevant to the progression of disease in the UK. However, resource use and cost estimates (a) are unlikely to be found in the published academic literature, and (b) must be

specific to the UK NHS. Similarly, transplantation rates and outcomes vary internationally and so UK values, even if based on smaller numbers than, for example, North American series, would be preferred.

Where possible, existing authoritative systematic reviews and meta-analyses will be used to inform the model. In some cases, it may be appropriate to carry out quantitative synthesis (e.g. of epidemiological studies of progression to HCC). Random effects models will generally be used in such cases, unless heterogeneity is minimal. The choice of outcome measure and appropriate statistical approach will be dependent on the type of data to be synthesised.

Costs will be taken from routine sources (i.e. generally top-down methods), principally the National Schedule of Reference Costs and Unit Costs of Health and Social Care,<sup>435</sup> based on Healthcare Resource Groups and other units. In some cases, notably diagnostic tests, unit costs may not be readily available from routine sources, and values from previous studies (appropriately inflated) or from individual NHS trusts may be required. Assumptions regarding resource use will be made explicit. Costs will be valued from the perspective of the NHS and based on 2004 values. Costs and benefits will be discounted at 3.5% in line with UK Treasury guidance.

### Outputs

For each of the comparisons given above, model outputs will be:

- number needed to monitor to prevent one death from HCC
- number needed to monitor to prevent one death (all causes)
- total cost of surveillance
- incremental cost per additional operable case of HCC identified by surveillance
- incremental cost per QALY.

The cost utility of each strategy to be compared will be plotted on a cost-effectiveness plane and options subject to dominance or extended dominance identified. The incremental cost-effectiveness of the remaining options will then be described based on a deterministic analysis.

### Analysis of uncertainty

A series of one-way sensitivity analyses will be carried out to identify the influence on model outputs of individual parameter inputs, holding all other inputs constant. In some cases parameters

## Project timetable

Week beginning	Task
12 September	Define search criteria and send to Southampton Health Technology Assessment Centre (Information Scientist)
19 September to 3 October	Set up Reference Manager database Assess search results and apply inclusion and exclusion criteria Request eligible papers
3 October to 24 October	Data extraction and checking
24 October to 5 December	Development of economic model
24 October to 20 February	Draft report
5 December to 6 February	Generate and interpret results
20 February	First complete draft to external advisory group
6 March to 31 March	Tabulate and incorporate changes Formatting and referencing checks
31 March	Deadline for submission

## Project team

Name	Title	Role
Dr Rob Anderson <sup>1</sup>	Senior Lecturer in Health Economics	Project direction, economic evaluation
Dr Jo Thompson Coon <sup>1</sup>	Research Fellow in Health Technology Assessment	Project management, systematic review, report preparation
Dr Matthew Cramp <sup>2</sup>	Senior Lecturer in Hepatology	Clinical advice
Mr Paul Hewson <sup>3</sup>	Senior Lecturer in Statistics	Decision-analytic model
Dr Simon Jackson <sup>4</sup>	Consultant Gastrointestinal Radiologist	Clinical advice
Ms Alison Price <sup>5</sup>	Information Scientist	Literature search and retrieval
Dr Steve Ryder <sup>6</sup>	Senior Lecturer in Hepatology	Clinical advice
Mr Gabriel Rogers <sup>1</sup>	Research Assistant in Health Technology Assessment	Project support, systematic review
Dr Ken Stein <sup>1</sup>	Senior Lecturer in Public Health	Study design, report preparation, methodological advice
Dr Dave Wright <sup>3</sup>	Reader in Applied Medical Statistics	Decision-analytic model

<sup>1</sup> Peninsula Technology Assessment Group, Peninsula Medical School  
<sup>2</sup> Hepatology Research Group, Peninsula Medical School  
<sup>3</sup> School of Mathematics and Statistics, University of Plymouth  
<sup>4</sup> Plymouth NHS Hospitals Trust, Plymouth  
<sup>5</sup> Southampton Health Technology Assessment Centre  
<sup>6</sup> Queen's Medical Centre, University of Nottingham

may be varied together to reflect plausible scenarios. For example, if appropriate data can be identified within the constraints of the project, we may explore the potential impact of using contrast enhanced ultrasound scanning by adjusting assumptions on test performance and cost.

In addition, a Bayesian approach to the analysis of uncertainty inherent in the model will be taken

within the framework of MCMC. A probabilistic sensitivity analysis will be carried out, in which parameter inputs will be drawn at random from appropriate distributions in a series of (at least 10,000) model 'runs'. The resultant series of incremental cost-effectiveness ratios (ICERs) will be plotted on a cost-effectiveness plane and used to generate a cost-effectiveness acceptability curve. This shows, for a range of values which service

commissioners (or the public) might be willing to pay for an additional unit of outcome (in this case a QALY), the probability that a strategy would be cost-effective.

The probabilistic analysis will also yield an estimate of the expected value of perfect information (EVPI) at the level of the cohort or individual patient. An estimate for the EVPI to the target population will be obtained by multiplying the patient level EVPI by the size of the

population in England and Wales who may be subject to surveillance and the expected time horizon for surveillance programmes in the UK. These two parameters are also uncertain and the range of values for the population EVPI which may be obtained from varying these inputs within plausible ranges will be explored. The contribution of selected parameter uncertainty to EVPI will be explored through estimation of partial EVPI and grouping of parameters where appropriate (to reduce computational expense).

## Appendix 2

### Systematic review: search strategies

#### Clinical searches

##### Cochrane Library (CDSR), Issue 3/2005

Search date: 13 July 2005

No. retrieved: 3; no. downloaded: 1

- #1 MeSH descriptor Liver Cirrhosis explode all trees in MeSH products (1412)
- #2 (cirrhosis NEAR liver\*) in All Fields in all products (2081)
- #3 MeSH descriptor Carcinoma, Hepatocellular explode all trees in MeSH products (419)
- #4 ((hepatocellular NEAR carcinoma\*) or HCC or hepatoma\*) in All Fields in all products (824)
- #5 MeSH descriptor Liver Neoplasms explode all trees in MeSH products (908)
- #6 (#1 OR #2 OR #3 OR #4 OR #5) (3157)
- #7 MeSH descriptor alpha-Fetoproteins explode all trees in MeSH products (89)
- #8 ((alfa?fetoprotein\* or alpha fetoprotein\* or AFP) NEAR (test\*)) in All Fields in all products (20)
- #9 ((liver NEAR ultrasound) or (liver NEAR ultrasonograph\*) or LUS) in All Fields in all products (200)
- #10 MeSH descriptor Liver explode all trees with qualifier: US in MeSH products (29)
- #11 (#7 OR #8 OR #9 OR #10) (295)
- #12 MeSH descriptor Mass Screening explode all trees in MeSH products (2580)
- #13 (surveillanc\* or screen\*) in All Fields in all products (12635)
- #14 (#12 OR #13) (12771)
- #15 (#6 AND #11 AND #14) (25)

##### Cochrane Library (CENTRAL), Issue 3/2005

Search date: 13 July 2005

No. retrieved: 13; no. downloaded: 8

Search strategy as above

##### BIOSIS (meeting abstracts); limited from 2002

Search date: 13 July 2005

No. retrieved: 48; no. downloaded: 14

((((al: (surveillanc\* or screen\*)) and ((al: (alpha fetoprotein\* OR AFP) or al: ((liver w5 ultrasound\*) or LUS) or al: ((liver w5

ultrasonograph\*) )) and ((al: (cirrhosis\*) or al: ((hepatocellular w5 carcinoma\*) or HCC ) or al: (hepatoma\*))))

##### NHS-CRD databases

(HTA/DARE/NHSEED)

Search date: 13 July 2005

No. downloaded: 7

(surveillanc\* or screen\*) AND (cirrhosis\* OR hepatocellular carcinoma\*)

##### Medline (OVID); 1966 to July week 1 2005

Search date: 18 July 2005

No. retrieved: 52 RCTs, 3 SRs;

no. downloaded: 51 RCTs, 2 SRs

- 1 exp Liver Cirrhosis/ (46034)
- 2 exp FIBROSIS/ (9445)
- 3 (cirrhosis adj4 liver\$.tw. (18245)
- 4 1 or 2 or 3 (60590)
- 5 exp Carcinoma, Hepatocellular/ (33454)
- 6 ((hepatocellular adj2 carcinoma\$) or HCC or hepatoma\$.tw. (38621)
- 7 Liver Neoplasms/ (66684)
- 8 5 or 6 or 7 (82535)
- 9 exp fetal proteins/ or exp alpha-fetoproteins/ (13045)
- 10 ((alfa?fetoprotein\$ or alpha?fetoprotein\$ or AFP) adj5 (test\$ or exam\$)).tw. (716)
- 11 9 or 10 (13227)
- 12 exp Ultrasonography/ec [Economics] (862)
- 13 LIVER/us [Ultrasonography] (1767)
- 14 ((liver adj5 ultrasound) or (liver adj5 ultrasonograph\$) or LUS).tw. (3140)
- 15 12 or 13 or 14 (5348)
- 16 exp Mass Screening/ (69340)
- 17 (surveillanc\$ or screen\$ or predict\$).ti,ab. (607761)
- 18 16 or 17 (635185)
- 19 (11 or 15) and 18 (2899)
- 20 19 and (4 or 8) (628)
- 21 limit 20 to (humans and english language) (506)
- 22 RANDOMIZED CONTROLLED TRIAL.pt. (202468)
- 23 CONTROLLED CLINICAL TRIAL.pt. (68612)
- 24 RANDOMIZED CONTROLLED TRIALS.sh. (37741)

- 25 RANDOM ALLOCATION.sh. (53250)  
 26 DOUBLE BLIND METHOD.sh. (81967)  
 27 SINGLE BLIND METHOD.sh. (9036)  
 28 or/22-27 (344270)  
 29 CLINICAL TRIAL.pt. (408163)  
 30 exp CLINICAL TRIALS/ (166723)  
 31 (clin\$ adj25 trial\$.ti,ab. (110895)  
 32 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25  
 (blind\$ or mask\$)).ti,ab. (81224)  
 33 PLACEBOS.sh. (23783)  
 34 placebo\$.ti,ab. (89091)  
 35 random\$.ti,ab. (311136)  
 36 RESEARCH DESIGN.sh. (40906)  
 37 or/29-36 (730854)  
 38 28 or 37 (751472)  
 39 38 and 21 (52)  
 40 (review or review-tutorial or review-  
 academic).pt. (1113269)  
 41 (Medline or medlars or embase).ti,ab,sh.  
 (17864)  
 42 (scisearch or psychinfo or psycinfo).ti,ab,sh.  
 (746)  
 43 (Psychlit or psyclit).ti,ab,sh. (619)  
 44 cinahl.ti,ab,sh. (1379)  
 45 ((hand adj59 search\$) or (manual\$ adj9  
 search\$)).mp. [mp=title, original title,  
 abstract, name of substance word, subject  
 heading word] (3281)  
 46 (electronic database\$ or bibliographic  
 database\$ or computeri#ed database\$ or  
 online database\$).mp. [mp=title, original title,  
 abstract, name of substance word, subject  
 heading word] (2976)  
 47 (pooling or pooled or mantel haenszel).mp.  
 [mp=title, original title, abstract, name of  
 substance word, subject heading word]  
 (21773)  
 48 (peto or dersimonian or der simonian or fixed  
 effect).mp. [mp=title, original title, abstract,  
 name of substance word, subject heading word]  
 (819)  
 49 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48  
 (42355)  
 50 40 and 49 (14239)  
 51 meta-analysis.pt. (10825)  
 52 meta-analysis.sh. (6007)  
 53 (meta-analys\$ or meta analys\$ or  
 metaanalys\$).mp. [mp=title, original title,  
 abstract, name of substance word, subject  
 heading word] (16105)  
 54 (systematic\$ adj9 review\$).mp. [mp=title,  
 original title, abstract, name of substance word,  
 subject heading word] (9254)  
 55 (systematic\$ adj9 overview\$).mp. [mp=title,  
 original title, abstract, name of substance word,  
 subject heading word] (380)

- 56 (quantitativ\$ adj9 review\$).mp. (1994)  
 57 (quantitativ\$ adj9 overview\$).mp. [mp=title,  
 original title, abstract, name of substance word,  
 subject heading word] (167)  
 58 (quantitativ\$ adj9 synthesis\$).mp. (1831)  
 59 (methodologic\$ adj9 review\$).mp. (2780)  
 60 (methodologic\$ adj9 overview\$).mp. (181)  
 61 (integrative research review\$ or research  
 integration).mp. (82)  
 62 or/51-61 (32368)  
 63 50 or 62 (42059)  
 64 63 and 21 (3)  
 65 39 not 64 (51)

### EMBASE (OVID); 1980 to 2005 week 29

Search date: 13 July 2005

No. retrieved: 132; no. downloaded: 98 RCTs

- 1 exp Liver Cirrhosis/ (34325)  
 2 (cirrhosis adj4 liver\$.ti,ab. (13772)  
 3 1 or 2 (37380)  
 4 exp Liver Cell Carcinoma/ (24446)  
 5 ((hepatocellular adj2 carcinoma\$) or HCC or  
 hepatoma\$.ti,ab. (31777)  
 6 Liver Tumors/ (0)  
 7 4 or 5 or 6 (36996)  
 8 alpha fetoproteins/ (9100)  
 9 ((alfa?f?etoprotein\$ or alpha?f?etoprotein\$ or  
 AFP) adj5 (test\$ or exam\$)).ti,ab. (596)  
 10 8 or 9 (9222)  
 11 ((liver adj5 ultrasound) or (liver adj5  
 ultrasonograph\$) or LUS).ti,ab. (2810)  
 12 exp echography/ (170673)  
 13 11 or 12 (171718)  
 14 exp Mass Screening/ or cancer screening/  
 (42438)  
 15 (surveillanc\$ or screen\$).ti,ab. (210941)  
 16 14 or 15 (223457)  
 17 (10 or 13) and 16 (9612)  
 18 17 and (3 or 7) (476)  
 19 limit 18 to (humans and english language)  
 (409)  
 20 randomization/ (15521)  
 21 controlled study/ (1983394)  
 22 single blind procedure/ (5384)  
 23 placebo/ (78761)  
 24 double blind procedure/ (56282)  
 25 clinical trial/ (342080)  
 26 crossover procedure/ (16380)  
 27 placebo\$.tw. (86301)  
 28 blind\$ fashion.tw. (3253)  
 29 random\$.tw. (279265)  
 30 clinical trial?.tw. (81431)  
 31 or/20-30 (2321729)  
 32 31 and 19 (132)

## PreMedline, Ovid MEDLINE(R), In-Process & Other Non-Indexed Citations

Search date: 15 July 2005

No. retrieved: 13; no. downloaded: 7

- 1 (cirrhosis adj4 liver\$.tw. (351)
- 2 ((hepatocellular adj2 carcinoma\$) or HCC or hepatoma\$.tw. (911)
- 3 ((alfa?f?etoprotein\$ or alpha?f?etoprotein\$ or AFP) adj5 (test\$ or exam\$)).tw. (9)
- 4 ((liver adj5 ultrasound) or (liver adj5 ultrasonograph\$) or LUS).tw. (67)
- 5 (surveillanc\$ or screen\$ or predict\$).ti,ab. (25822)
- 6 (clin\$ adj25 trial\$).ti,ab. (4131)
- 7 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab. (1589)
- 8 placebo\$.ti,ab. (2076)
- 9 random\$.ti,ab. (12663)
- 10 or/6-9 (16240)
- 11 1 or 2 (1162)
- 12 3 or 4 or 5 (25884)
- 13 11 and 12 (147)
- 14 13 and 10 (17)
- 15 limit 14 to english language (13)

## ISI Science Citation Index; 1970–2005

Search date: 13 July 2005

No. retrieved: 68; no. downloaded: 45

- #1 TS=(cirrhosis SAME liver\*)
- #2 TS=((hepatocellular SAME carcinoma\*) or HCC or hepatoma)
- #3 #1 or #2
- #4 TS=((alpha fetoprotein\* OR AFP)AND(test\*))
- #5 TS=((liver SAME ultrasound\*) or (liver SAME ultrasonograph\*) or LUS)
- #6 #4 or #5
- #7 TS=(surveillanc\* or screen\*)
- #8 #3 and #6 and #7

*DocType=All document types; Language=English*

## Web of Science Proceedings; 1990 to present

Search date: 13 July 2005

No. retrieved: 15; no. downloaded: 15

Search strategy as above

### Total clinical effectiveness refs: 185

Keyworded clinical effectiveness and RCTs: 136

Keyworded clinical effectiveness and SRs: 4

Keyworded conference proceedings: 20

## Cost-effectiveness searches

### MEDLINE (OVID)

No. retrieved: 32; no. downloaded: 32

- 1 exp Liver Cirrhosis/ (46034)
- 2 exp FIBROSIS/ (9445)
- 3 (cirrhosis adj4 liver\$.tw. (18245)
- 4 1 or 2 or 3 (60590)
- 5 exp Carcinoma, Hepatocellular/ (33454)
- 6 ((hepatocellular adj2 carcinoma\$) or HCC or hepatoma\$.tw. (38621)
- 7 Liver Neoplasms/ (66684)
- 8 5 or 6 or 7 (82535)
- 9 exp fetal proteins/ or exp alpha-fetoproteins/ (13045)
- 10 ((alfa?f?etoprotein\$ or alpha?f?etoprotein\$ or AFP) adj5 (test\$ or exam\$)).tw. (716)
- 11 9 or 10 (13227)
- 12 exp Ultrasonography/ec [Economics] (862)
- 13 LIVER/us [Ultrasonography] (1767)
- 14 ((liver adj5 ultrasound) or (liver adj5 ultrasonograph\$) or LUS).tw. (3140)
- 15 12 or 13 or 14 (5348)
- 16 exp Mass Screening/ (69340)
- 17 (surveillanc\$ or screen\$ or predict\$).ti,ab. (607761)
- 18 16 or 17 (635185)
- 19 (11 or 15) and 18 (2899)
- 20 19 and (4 or 8) (628)
- 21 limit 20 to (humans and english language) (506)
- 68 exp ECONOMICS/ (335296)
- 69 exp ECONOMICS, HOSPITAL/ (13361)
- 70 exp ECONOMICS, PHARMACEUTICAL/ (1472)
- 71 exp ECONOMICS, NURSING/ (3666)
- 72 exp ECONOMICS, DENTAL/ (3277)
- 73 exp ECONOMICS, MEDICAL/ (9656)
- 74 exp "Costs and Cost Analysis"/ (116153)
- 75 Cost-Benefit Analysis/ (35405)
- 76 VALUE OF LIFE/ (4470)
- 77 exp MODELS, ECONOMIC/ (4239)
- 78 exp FEES/ and CHARGES/ (6677)
- 79 exp BUDGETS/ (8809)
- 80 (economic\$ or price\$ or pricing or financ\$ or fee\$ or pharmacoeconomic\$ or pharma economic\$).tw. (278989)
- 81 (cost\$ or costly or costing\$ or costed).tw. (162320)
- 82 (cost\$ adj2 (benefit\$ or utilit\$ or minim\$ or effective\$)).tw. (43554)
- 83 (expenditure\$ not energy).tw. (8982)
- 84 (value adj2 (money or monetary)).tw. (517)
- 85 budget\$.tw. (9297)
- 86 (economic adj2 burden).tw. (1100)

- 87 "resource use".ti,ab. (21385)
- 88 or/68-86 (657491)
- 89 news.pt. (94154)
- 90 letter.pt. (530731)
- 91 editorial.pt. (174605)
- 92 comment.pt. (274228)
- 93 or/89-92 (828823)
- 94 88 not 93 (606583)
- 95 94 and 21 (38)
- 96 95 not 39 (32)

### EMBASE (OVID); 1980–2005 2005 week 29

No. retrieved: 45; no. downloaded: 45

- 1 exp Liver Cirrhosis/ (34325)
- 2 (cirrhosis adj4 liver\$).ti,ab. (13772)
- 3 1 or 2 (37380)
- 4 exp Liver Cell Carcinoma/ (24446)
- 5 ((hepatocellular adj2 carcinoma\$) or HCC or hepatoma\$).ti,ab. (31777)
- 6 Liver Tumors/ (0)
- 7 4 or 5 or 6 (36996)
- 8 alpha fetoproteins/ (9100)
- 9 ((alfa?f?etoprotein\$ or alpha?f?etoprotein\$ or AFP) adj5 (test\$ or exam\$)).ti,ab. (596)
- 10 8 or 9 (9222)
- 11 ((liver adj5 ultrasound) or (liver adj5 ultrasonograph\$) or LUS).ti,ab. (2810)
- 12 exp echography/ (170673)
- 13 11 or 12 (171718)
- 14 exp Mass Screening/ or cancer screening/ (42438)
- 15 (surveillanc\$ or screen\$).ti,ab. (210941)
- 16 14 or 15 (223457)
- 17 (10 or 13) and 16 (9612)
- 18 17 and (3 or 7) (476)
- 19 limit 18 to (humans and english language) (409)
- 20 (cost\$ adj2 effective\$).ti,ab. (31805)
- 21 (cost\$ adj2 benefit\$).ti,ab. (7885)
- 22 cost effectiveness analysis/ (38873)
- 23 cost benefit analysis/ (21072)
- 24 budget\$.ti,ab. (6851)
- 25 cost\$.ti. (30014)
- 26 (cost\$ adj2 (effective\$ or utilit\$ or benefit\$ or minimi\$)).ab. (35613)
- 27 (economic\$ or pharmaco-economic\$ or pharmaco economic\$).ti. (11649)
- 28 (price\$ or pricing\$).ti,ab. (8549)
- 29 (financial or finance or finances or financed).ti,ab. (17644)
- 30 (fee or fees).ti,ab. (4163)
- 31 cost/ (17601)
- 32 cost minimization analysis/ (838)
- 33 cost of illness/ (2567)
- 34 cost utility analysis/ (1355)

- 35 drug cost/ (24042)
- 36 health care cost/ (42269)
- 37 health economics/ (7601)
- 38 economic evaluation/ (2569)
- 39 economics/ (4651)
- 40 pharmaco-economic/ (839)
- 41 budget/ (5925)
- 42 economic burden.ti,ab. (1030)
- 43 "resource use".ti,ab. (16978)
- 44 or/20-43 (192296)
- 45 (editorial or letter).pt. (433125)
- 46 44 not 45 (173533)
- 47 46 and 19 (45)

### PubMed; Ovid MEDLINE(R), In-Process & Other Non-Indexed Citations

Search date: 15 July 2005

No. retrieved: 3; no. downloaded: 3

- 1 (cirrhosis adj4 liver\$).tw. (351)
- 2 ((hepatocellular adj2 carcinoma\$) or HCC or hepatoma\$).tw. (911)
- 3 ((alfa?f?etoprotein\$ or alpha?f?etoprotein\$ or AFP) adj5 (test\$ or exam\$)).tw. (9)
- 4 ((liver adj5 ultrasound) or (liver adj5 ultrasonograph\$) or LUS).tw. (67)
- 5 (surveillanc\$ or screen\$ or predict\$).ti,ab. (25822)
- 6 (clin\$ adj25 trial\$).ti,ab. (4131)
- 7 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab. (1589)
- 8 placebo\$.ti,ab. (2076)
- 9 random\$.ti,ab. (12663)
- 10 or/6-9 (16240)
- 11 1 or 2 (1162)
- 12 3 or 4 or 5 (25884)
- 13 11 and 12 (147)
- 14 limit 13 to english language (109)
- 15 (economic\$ or price\$ or pricing\$ or pharmaco-economic\$ or pharmaco-economic\$).tw. (2454)
- 16 (cost\$ or costly\$ or costing\$ or costed).tw. (5138)
- 17 (cost\$ adj2 (benefit\$ or utilit\$ or minim\$)).tw. (344)
- 18 (expenditure\$ not energy).tw. (205)
- 19 (value adj2 (money or monetary)).tw. (23)
- 20 budget\$.tw. (310)
- 21 (economic adj2 burden).tw. (71)
- 22 or/15-21 (7241)
- 23 14 and 22 (3)
- 24 from 23 keep 1-3 (3)

### Econlit

No. retrieved: 0; no. downloaded: 0

(surveillanc\* or screen\*) AND (cirrhosis\* OR hepatocellular carcinoma\*)



**NHS EED**

No. retrieved: 9; no. downloaded: 6  
Search strategy as run in Cochrane Library

**Total refs:** 17 (17 records keyworded both clinical effectiveness and cost-effectiveness)

**Updated clinical searches****Cochrane Library (CDSR), Issue 1/2006**

No. retrieved: 0; no. downloaded: 0  
MEDLINE search run

**Cochrane Library (CENTRAL), Issue 3/2005**

No. retrieved: 0; no. downloaded: 0  
MEDLINE search run

**Ovid MEDLINE(R); 1966 to March week 2 2006**

Search date: 20 March 2006  
No. retrieved: 11; no. downloaded: 11

- 1 exp Liver Cirrhosis/ (47211)
- 2 exp FIBROSIS/ (10155)
- 3 (cirrhosis adj4 liver\$).tw. (17234)
- 4 1 or 2 or 3 (62106)
- 5 exp Carcinoma, Hepatocellular/ (34811)
- 6 ((hepatocellular adj2 carcinoma\$) or HCC or hepatoma\$).tw. (39929)
- 7 Liver Neoplasms/ (69020)
- 8 5 or 6 or 7 (85236)
- 9 exp fetal proteins/ or exp alpha-fetoproteins/ (13218)
- 10 ((alfa?f?etoprotein\$ or alpha?f?etoprotein\$ or AFP) adj5 (test\$ or exam\$)).tw. (498)
- 11 9 or 10 (13337)
- 12 exp Ultrasonography/ec [Economics] (884)
- 13 LIVER/us [Ultrasonography] (1856)
- 14 ((liver adj5 ultrasound) or (liver adj5 ultrasonograph\$) or LUS).tw. (2346)
- 15 12 or 13 or 14 (4754)
- 16 exp Mass Screening/ (73163)
- 17 (surveillanc\$ or screen\$ or predict\$).ti,ab. (646968)
- 18 16 or 17 (675751)
- 19 (11 or 15) and 18 (2920)
- 20 19 and (4 or 8) (616)
- 21 limit 20 to (humans and english language) (506)
- 22 RANDOMIZED CONTROLLED TRIAL.pt. (213938)
- 23 CONTROLLED CLINICAL TRIAL.pt. (70827)
- 24 RANDOMIZED CONTROLLED TRIALS.sh. (41719)
- 25 RANDOM ALLOCATION.sh. (54818)
- 26 DOUBLE BLIND METHOD.sh. (85685)
- 27 SINGLE BLIND METHOD.sh. (9750)
- 28 or/22-27 (363742)
- 29 CLINICAL TRIAL.pt. (424238)
- 30 exp CLINICAL TRIALS/ (175708)
- 31 (clin\$ adj25 trial\$).ti,ab. (113981)
- 32 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab. (84254)
- 33 PLACEBOS.sh. (24604)
- 34 placebo\$.ti,ab. (94201)
- 35 random\$.ti,ab. (332233)
- 36 RESEARCH DESIGN.sh. (43231)
- 37 or/29-36 (771531)
- 38 28 or 37 (794492)
- 39 38 and 21 (56)
- 40 (review or review-tutorial or review-academic).pt. (1169826)
- 41 (Medline or medlars or embase).ti,ab,sh. (19974)
- 42 (scisearch or psychinfo or psycinfo).ti,ab,sh. (927)
- 43 (Psychlit or psyclit).ti,ab,sh. (662)
- 44 cinahl.ti,ab,sh. (1669)
- 45 ((hand adj59 search\$) or (manual\$ adj9 search\$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3307)
- 46 (electronic database\$ or bibliographic database\$ or computeri#ed database\$ or online database\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3382)
- 47 (pooling or pooled or mantel haenszel).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (23238)
- 48 (peto or dersimonian or der simonian or fixed effect).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (943)
- 49 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 (45899)
- 50 40 and 49 (16283)
- 51 meta-analysis.pt. (12428)
- 52 meta-analysis.sh. (6532)
- 53 (meta-analys\$ or meta analys\$ or metaanalys\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (22670)
- 54 (systematic\$ adj9 review\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (10302)
- 55 (systematic\$ adj9 overview\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (363)
- 56 (quantitativ\$ adj9 review\$).mp. (1523)

- 57 (quantitativ\$ adj9 overview\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (138)  
 58 (quantitativ\$ adj9 synthesis\$).mp. (1247)  
 59 (methodologic\$ adj9 review\$).mp. (2198)  
 60 (methodologic\$ adj9 overview\$).mp. (138)  
 61 (integrative research review\$ or research integration).mp. (47)  
 62 or/51-61 (33941)  
 63 50 or 62 (44747)  
 64 63 and 21 (5)  
 65 39 not 64 (54)  
 66 39 (56)  
 67 limit 66 to yr="2005 - 2006" (9)  
 68 64 (5)  
 69 limit 68 to yr="2005 - 2006" (3)  
 70 67 or 69 (11)

**EMBASE; 1996 to 2006 week 11**

No. retrieved: 22; no. downloaded: 22

- 1 exp Liver Cirrhosis/ (19458)
- 2 (cirrhosis adj4 liver\$).ti,ab. (7537)
- 3 1 or 2 (20775)
- 4 exp Liver Cell Carcinoma/ (15876)
- 5 ((hepatocellular adj2 carcinoma\$) or HCC or hepatoma\$).ti,ab. (18538)
- 6 Liver Tumors/ (0)
- 7 4 or 5 or 6 (21806)
- 8 alpha fetoproteins/ (4716)
- 9 ((alfa?f?etoprotein\$ or alpha?f?etoprotein\$ or AFP) adj5 (test\$ or exam\$)).ti,ab. (256)
- 10 8 or 9 (4774)
- 11 ((liver adj5 ultrasound) or (liver adj5 ultrasonograph\$) or LUS).ti,ab. (1738)
- 12 exp echography/ (113303)
- 13 11 or 12 (113959)
- 14 exp Mass Screening/ or cancer screening/ (35235)
- 15 (surveillanc\$ or screen\$).ti,ab. (147186)
- 16 14 or 15 (157420)
- 17 (10 or 13) and 16 (7165)
- 18 17 and (3 or 7) (358)
- 19 limit 18 to (humans and english language) (304)
- 20 randomization/ (16400)
- 21 controlled study/ (1570222)
- 22 single blind procedure/ (4865)
- 23 placebo/ (46574)
- 24 double blind procedure/ (40232)
- 25 clinical trial/ (303293)
- 26 crossover procedure/ (13291)
- 27 placebo\$.tw. (50473)
- 28 blind\$ fashion.tw. (1807)
- 29 random\$.tw. (197574)
- 30 clinical trial?.tw. (61214)
- 31 or/20-30 (1801240)
- 32 31 and 19 (124)

- 33 32 (124)  
 34 limit 33 to yr="2005 - 2006" (22)

**Ovid MEDLINE(R), In-Process & Other Non-Indexed Citations**

Search date: 17 March 2006

No. retrieved: 6; no. downloaded: 6

- 1 (cirrhosis adj4 liver\$).tw. (340)
- 2 ((hepatocellular adj2 carcinoma\$) or HCC or hepatoma\$).tw. (1014)
- 3 ((alfa?f?etoprotein\$ or alpha?f?etoprotein\$ or AFP) adj5 (test\$ or exam\$)).tw. (10)
- 4 ((liver adj5 ultrasound) or (liver adj5 ultrasonograph\$) or LUS).tw. (64)
- 5 (surveillanc\$ or screen\$ or predict\$).ti,ab. (30246)
- 6 (clin\$ adj25 trial\$).ti,ab. (4424)
- 7 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab. (1623)
- 8 placebo\$.ti,ab. (2171)
- 9 random\$.ti,ab. (14665)
- 10 or/6-9 (18489)
- 11 1 or 2 (1269)
- 12 3 or 4 or 5 (30298)
- 13 11 and 12 (150)
- 14 13 and 10 (11)
- 15 limit 14 to english language (6)

**ISI Science Citation Index; 1970–2005**

No. retrieved: 16; no. downloaded: 21

- #1 TS=(cirrhosis SAME liver\*) (1,260)
- #2 TS=((hepatocellular SAME carcinoma\*) or HCC or hepatoma) (4,362)
- #3 #1 or #2 (5,243)
- #4 TS=((alpha fetoprotein\* OR AFP)AND(test\*)) (118)
- #5 TS=((liver SAME ultrasound\*) or (liver SAME ultrasonograph\*) or LUS) (303)
- #6 #4 or #5 (419)
- #7 TS=(surveillanc\* or screen\*) (32,290)
- #8 #3 and #6 and #7 (21)

*DocType=All document types; Language=English;  
 Database=SCI-EXPANDED; Timespan=2005-2006*

**Total updated clinical effectiveness refs: 29****Updated cost-effectiveness searches****Ovid MEDLINE (R); 1996 to March week 2 2006**

Search date: 20 March 2006

No. retrieved: 2; no. downloaded: 1

- 1 exp Liver Cirrhosis/ (14393)
- 2 exp FIBROSIS/ (6056)
- 3 (cirrhosis adj4 liver\$.tw. (6667)
- 4 1 or 2 or 3 (22882)
- 5 exp Carcinoma, Hepatocellular/ (15593)
- 6 ((hepatocellular adj2 carcinoma\$) or HCC or hepatoma\$.tw. (18850)
- 7 Liver Neoplasms/ (26942)
- 8 5 or 6 or 7 (34391)
- 9 exp fetal proteins/ or exp alpha-fetoproteins/ (3560)
- 10 ((alfa?fetoprotein\$ or alpha?fetoprotein\$ or AFP) adj5 (test\$ or exam\$)).tw. (181)
- 11 9 or 10 (3627)
- 12 exp Ultrasonography/ec [Economics] (599)
- 13 LIVER/us [Ultrasonography] (1212)
- 14 ((liver adj5 ultrasound) or (liver adj5 ultrasonograph\$) or LUS).tw. (1287)
- 15 12 or 13 or 14 (2872)
- 16 exp Mass Screening/ (40588)
- 17 (surveillanc\$ or screen\$).ti,ab. (154472)
- 18 16 or 17 (169987)
- 19 (11 or 15) and 18 (977)
- 20 19 and (4 or 8) (183)
- 21 limit 20 to (humans and english language) (143)
- 22 RANDOMIZED CONTROLLED TRIAL.pt. (117366)
- 23 CONTROLLED CLINICAL TRIAL.pt. (25106)
- 24 RANDOMIZED CONTROLLED TRIALS.sh. (33317)
- 25 RANDOM ALLOCATION.sh. (19806)
- 26 DOUBLE BLIND METHOD.sh. (40674)
- 27 SINGLE BLIND METHOD.sh. (7145)
- 28 or/22-27 (197624)
- 29 CLINICAL TRIAL.pt. (220803)
- 30 exp CLINICAL TRIALS/ (81478)
- 31 (clin\$ adj25 trial\$).ti,ab. (73095)
- 32 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab. (39471)
- 33 PLACEBOS.sh. (7140)
- 34 placebo\$.ti,ab. (49063)
- 35 random\$.ti,ab. (205145)
- 36 RESEARCH DESIGN.sh. (21607)
- 37 or/29-36 (447524)
- 38 28 or 37 (461568)
- 39 38 and 21 (21)
- 40 (review or review-tutorial or review-academic).pt. (643186)
- 41 (Medline or medlars or embase).ti,ab,sh. (16873)
- 42 (scisearch or psychinfo or psycinfo).ti,ab,sh. (879)
- 43 (Psychlit or psyclit).ti,ab,sh. (631)
- 44 cinahl.ti,ab,sh. (1599)
- 45 ((hand adj59 search\$) or (manual\$ adj9 search\$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2706)
- 46 (electronic database\$ or bibliographic database\$ or computeri#ed database\$ or online database\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2932)
- 47 (pooling or pooled or mantel haenszel).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (12886)
- 48 (peto or dersimonian or der simonian or fixed effect).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (803)
- 49 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 (31739)
- 50 40 and 49 (14557)
- 51 meta-analysis.pt. (10053)
- 52 meta-analysis.sh. (4533)
- 53 (meta-analys\$ or meta analys\$ or metaanalys\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (18382)
- 54 (systematic\$ adj9 review\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (9570)
- 55 (systematic\$ adj9 overview\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (296)
- 56 (quantitativ\$ adj9 review\$).mp. (1004)
- 57 (quantitativ\$ adj9 overview\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (88)
- 58 (quantitativ\$ adj9 synthesis\$).mp. (471)
- 59 (methodologic\$ adj9 review\$).mp. (1533)
- 60 (methodologic\$ adj9 overview\$).mp. (88)
- 61 (integrative research review\$ or research integration).mp. (27)
- 62 or/51-61 (27129)
- 63 50 or 62 (36464)
- 64 63 and 21 (3)
- 65 39 not 64 (19)
- 66 from 64 keep 1-2 (2)
- 67 [from 65 keep 1-28] (0)
- 68 exp ECONOMICS/ (151088)
- 69 exp ECONOMICS, HOSPITAL/ (5633)
- 70 exp ECONOMICS, PHARMACEUTICAL/ (1257)
- 71 exp ECONOMICS, NURSING/ (340)
- 72 exp ECONOMICS, DENTAL/ (453)
- 73 exp ECONOMICS, MEDICAL/ (1494)
- 74 exp "Costs and Cost Analysis"/ (60722)
- 75 Cost-Benefit Analysis/ (21978)
- 76 VALUE OF LIFE/ (1526)
- 77 exp MODELS, ECONOMIC/ (3516)
- 78 exp FEES/ and CHARGES/ (2065)
- 79 exp BUDGETS/ (4528)

- 80 (economic\$ or price\$ or pricing or financ\$ or fee\$ or pharmacoeconomic\$ or pharma economic\$.tw. (146112)
- 81 (cost\$ or costly or costing\$ or costed).tw. (101507)
- 82 (cost\$ adj2 (benefit\$ or utilit\$ or minim\$ or effective\$)).tw. (28642)
- 83 (expenditure\$ not energy).tw. (5188)
- 84 (value adj2 (money or monetary)).tw. (328)
- 85 budget\$.tw. (5078)
- 86 (economic adj2 burden).tw. (978)
- 87 "resource use".ti,ab. (1400)
- 88 or/68-86 (330559)
- 89 news.pt. (63130)
- 90 letter.pt. (244785)
- 91 editorial.pt. (105133)
- 92 comment.pt. (200391)
- 93 or/89-92 (440426)
- 94 88 not 93 (300499)
- 95 94 and 21 (24)
- 96 95 not 39 (19)
- 97 95 (24)
- 98 limit 97 to yr="2005 - 2006" (2)
- 99 from 98 keep 2 (1)

**EMBASE; 1996 to 2006 week 11**

No. retrieved: 8; no. downloaded: 8

- 1 exp Liver Cirrhosis/ (19458)
- 2 (cirrhosis adj4 liver\$.ti,ab. (7537)
- 3 1 or 2 (20775)
- 4 exp Liver Cell Carcinoma/ (15876)
- 5 ((hepatocellular adj2 carcinoma\$) or HCC or hepatoma\$.ti,ab. (18538)
- 6 Liver Tumors/ (0)
- 7 4 or 5 or 6 (21806)
- 8 alpha fetoproteins/ (4716)
- 9 ((alfa?f?etoprotein\$ or alpha?f?etoprotein\$ or AFP) adj5 (test\$ or exam\$)).ti,ab. (256)
- 10 8 or 9 (4774)
- 11 ((liver adj5 ultrasound) or (liver adj5 ultrasonograph\$) or LUS).ti,ab. (1738)
- 12 exp echography/ (113303)
- 13 11 or 12 (113959)
- 14 exp Mass Screening/ or cancer screening/ (35235)
- 15 (surveillanc\$ or screen\$).ti,ab. (147186)
- 16 14 or 15 (157420)
- 17 (10 or 13) and 16 (7165)
- 18 17 and (3 or 7) (358)
- 19 limit 18 to (humans and english language) (304)
- 20 (cost\$ adj2 effective\$).ti,ab. (24424)
- 21 (cost\$ adj2 benefit\$).ti,ab. (5067)
- 22 cost effectiveness analysis/ (34291)
- 23 cost benefit analysis/ (17303)
- 24 budget\$.ti,ab. (4317)
- 25 cost\$.ti. (19912)

- 26 (cost\$ adj2 (effective\$ or utilit\$ or benefit\$ or minimi\$)).ab. (26986)
- 27 (economic\$ or pharmacoeconomic\$ or pharmaco economic\$.ti. (8024)
- 28 (price\$ or pricing\$).ti,ab. (5556)
- 29 (financial or finance or finances or financed).ti,ab. (11828)
- 30 (fee or fees).ti,ab. (2689)
- 31 cost/ (8727)
- 32 cost minimization analysis/ (941)
- 33 cost of illness/ (3022)
- 34 cost utility analysis/ (1564)
- 35 drug cost/ (20646)
- 36 health care cost/ (37786)
- 37 health economics/ (6265)
- 38 economic evaluation/ (2975)
- 39 economics/ (2307)
- 40 pharmacoeconomics/ (795)
- 41 budget/ (5287)
- 42 economic burden.ti,ab. (1020)
- 43 "resource use".ti,ab. (13875)
- 44 or/20-43 (144559)
- 45 (editorial or letter).pt. (313737)
- 46 44 not 45 (128769)
- 47 46 and 19 (39)
- 48 47 (39)
- 49 limit 48 to yr="2005 - 2006" (8)

**Ovid MEDLINE(R), In-Process & Other Non-Indexed Citations**

Search date: 17 March 2006

No. retrieved: 4; no. downloaded: 2

- 1 (cirrhosis adj4 liver\$.tw. (340)
- 2 ((hepatocellular adj2 carcinoma\$) or HCC or hepatoma\$.tw. (1014)
- 3 ((alfa?f?etoprotein\$ or alpha?f?etoprotein\$ or AFP) adj5 (test\$ or exam\$)).tw. (10)
- 4 ((liver adj5 ultrasound) or (liver adj5 ultrasonograph\$) or LUS).tw. (64)
- 5 (surveillanc\$ or screen\$ or predict\$).ti,ab. (30246)
- 6 (clin\$ adj25 trial\$).ti,ab. (4424)
- 7 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab. (1623)
- 8 placebo\$.ti,ab. (2171)
- 9 random\$.ti,ab. (14665)
- 10 or/6-9 (18489)
- 11 1 or 2 (1269)
- 12 3 or 4 or 5 (30298)
- 13 11 and 12 (150)
- 14 13 and 10 (11)
- 15 limit 14 to english language (6)
- 16 from 15 keep 1-6 (6)
- 17 (economic\$ or price\$ or pricing or pharmacoeconomic\$ or pharma economic\$.tw. (2958)

- 18 (cost\$ or budget\$).tw. (6208)
- 19 (cost\$ adj2 (benefit\$ or utilit\$ or minim\$)).tw. (319)
- 20 (value adj2 (money or monetary)).tw. (22)
- 21 17 or 18 or 19 or 20 (8386)
- 22 21 and 13 (4)
- 23 from 22 keep 1,3 (2)

### NHS EED in Cochrane Library Issue 1/2006

No. retrieved: 7; no. downloaded: 7

- #1 MeSH descriptor Liver Cirrhosis explode all trees in MeSH products (1470)
- #2 (cirrhosis NEAR liver\*) in All Fields in all products (2186)
- #3 MeSH descriptor Carcinoma, Hepatocellular explode all trees in MeSH products (455)
- #4 ((hepatocellular NEAR carcinoma\*) or HCC or hepatoma\*) in All Fields in all products (898)
- #5 MeSH descriptor Liver Neoplasms explode all trees in MeSH products (971)
- #6 (#1 OR #2 OR #3 OR #4 OR #5) (3336)
- #7 MeSH descriptor alpha-Fetoproteins explode all trees in MeSH products (94)
- #8 ((alfa?fetoprotein\* or alpha fetoprotein\* or AFP) NEAR (test\*)) in All Fields in all products (23)
- #9 ((liver NEAR ultrasound) or (liver NEAR ultrasonograph\*) or LUS) in All Fields in all products (216)
- #10 MeSH descriptor Liver explode all trees with qualifier: US in MeSH products (30)
- #11 (#7 OR #8 OR #9 OR #10) (314)
- #12 MeSH descriptor Mass Screening explode all trees in MeSH products (2805)
- #13 (surveillanc\* or screen\*) in All Fields in all products (13858)
- #14 (#12 OR #13) (14000)
- #15 (#6 AND #11 AND #14) (29)
- #16 (#15), from 2005 to 2006 (7)

Total updated cost-effectiveness refs: 7

### Parameter searches: natural history of cirrhosis and HCC

#### MEDLINE (OVID)

No. downloaded: 131

- 1 \*Carcinoma, Hepatocellular/mo, ep, et [Mortality, Epidemiology, Etiology] (1698)
- 2 exp Epidemiology/sn [Statistics & Numerical Data] (164)

- 3 exp morbidity/ or incidence/ or prevalence/ or survival rate/ (239036)
- 4 "Prognosis"/ (216344)
- 5 2 or 3 or 4 (431317)
- 7 1 and 5 (459)
- 8 limit 7 to (english language and yr="2002 - 2005") (131)

### Embase (OVID) 1980– Keyworded HCC NATURAL HISTORY

No. downloaded: 50

- 1 \*Liver Cell Carcinoma/et, ep [Etiology, Epidemiology] (2314)
- 2 ((natural histor\$ or survival or disease course or disease progress\$) adj4 (cirrhosis or hepatocellular carcinoma\$ or HCC or hepatoma)).ti,ab. (1091)
- 3 1 and 2 (172)
- 4 exp morbidity/ or incidence/ or prevalence/ or survival rate/ (178541)
- 5 "Prognosis"/ (89427)
- 6 4 or 5 (255124)
- 7 3 and 6 (96)
- 8 limit 7 to english language (94)
- 9 limit 8 to yr="2002 - 2005" (50)

### Ovid MEDLINE(R), In-Process & Other Non-Indexed Citations; 29 July 2005

No. downloaded: 62

- 1 ((natural histor\$ or survival or disease course or disease progress\$) adj4 (cirrhosis or hepatocellular carcinoma\$ or HCC or hepatoma)).ti,ab. (66)
- 2 incidence.ti. (720)
- 3 prevalence.ti. (1071)
- 4 epidemiol\$.ti. (868)
- 5 (etiolog\$ or aetiolog\$).ti. (281)
- 6 or/2-5 (2884)
- 7 (cirrhosis or hepatocellular carcinoma\$ or HCC or hepatoma).mp. [mp=title, original title, abstract, name of substance word] (1419)
- 8 6 and 7 (18)
- 9 1 or 8 (82)
- 10 limit 9 to english language (62)

Total refs in database after deduplication: 196

### Parameter searches: effectiveness of treatments for HCC

#### Cochrane Library (CDSR); 2005 Issue 3

No. retrieved: 6; no. downloaded: CDSR 1

MEDLINE strategy run

**Cochrane Library (CENTRAL); 2004 Issue 4**

No. downloaded: CENTRAL 86

**MEDLINE (OVID)**

No. downloaded: 214

- 1 \*"Carcinoma, Hepatocellular"/th [Therapy] (2137)
- 2 "Catheter Ablation"/mt [Methods] (2379)
- 3 "Embolization, Therapeutic"/mt [Methods] (4109)
- 4 \*"Liver Neoplasms"/th [Therapy] (3435)
- 5 "Liver Transplantation"/mt [Methods] (3006)
- 6 "Mass Screening"/mt [Methods] (10902)
- 7 metastectomy.ti,ab. (19)
- 8 metastasectomy.ti,ab. (329)
- 9 ((hepatic adj5 resection) or hepatectomy).ti,ab. (11166)
- 10 (liver adj5 transplant\$.ti,ab. (24529)
- 11 (tumo?r adj3 resection\$.ti,ab. (11523)
- 12 or/2-11 (66292)
- 13 12 and 1 (2043)
- 14 limit 13 to (humans and english language) (1308)
- 15 (clinical trial or meta analysis or clinical trial phase i or multicenter study or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv or practice guideline or controlled clinical trial or randomized controlled trial or "review multicase" or evaluation studies or guideline).pt. (520658)
- 16 14 and 15 (214)

**PreMedline**

No. retrieved: 6; no. downloaded: 6

- 1 ((hepatic adj5 resection) or hepatectomy).ti,ab. (221)
- 2 (liver adj5 transplant\$.ti,ab. (835)
- 3 ((tumo?r or liver) adj3 resect\$.ti,ab. (550)
- 4 1 or 2 or 3 (1481)
- 5 (cirrhosis adj4 liver\$.tw. (351)
- 6 ((hepatocellular adj2 carcinoma\$) or HCC or hepatoma\$.tw. (935)
- 7 5 or 6 (1182)
- 8 (clin\$ adj25 trial\$.ti,ab. (4317)
- 9 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab. (1599)
- 10 placebo\$.ti,ab. (2101)
- 11 random\$.ti,ab. (13117)
- 12 or/8-11 (16872)
- 13 4 and 6 (146)
- 14 13 and 12 (8)
- 15 limit 14 to english language (6)

**EMBASE (OVID)**

No. downloaded: SRs 6, RCTs 145, cohorts 24

- 1 \*"Carcinoma, Hepatocellular"/th [Therapy] (1488)
- 2 \*"Liver Neoplasms"/th [Therapy] (268)
- 3 ((hepatic adj5 resection) or hepatectomy).ti,ab. (8784)
- 4 (liver adj5 transplant\$.ti,ab. (22570)
- 5 exp liver transplantation/ (25595)
- 6 ((tumo?r or liver) adj3 resect\$.ti,ab. (17018)
- 7 1 or 2 (1745)
- 8 3 or 4 or 5 or 6 (51897)
- 9 7 and 8 (425)
- 10 limit 9 to (human and english language) (339)
- 11 randomization/ (15584)
- 12 controlled study/ (1987067)
- 13 single blind procedure/ (5394)
- 14 placebo/ (78929)
- 15 double blind procedure/ (56354)
- 16 clinical trial/ (342808)
- 17 crossover procedure/ (16404)
- 18 placebo\$.tw. (86404)
- 19 blind\$ fashion.tw. (3256)
- 20 random\$.tw. (279745)
- 21 clinical trial?.tw. (81593)
- 22 or/11-21 (2326047)
- 23 limit 22 to human (1460045)
- 24 23 and 10 (145)
- 25 exp meta analysis/ (22268)
- 26 meta#analy\$.ab,sh,ti. (22269)
- 27 methodologic\$ review\$.ab,sh,ti. (115)
- 28 methodologic\$ overview\$.ab,sh,ti. (27)
- 29 (integrative research adj5 review\$.mp. or research integration.ab,ti. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (46)
- 30 quantitat\$ synthesis.ab,sh,ti. (84)
- 31 quantitat\$ review\$.ab,sh,ti. (224)
- 32 quantitat\$ overview\$.ab,sh,ti. (58)
- 33 systematic\$ review\$.ab,sh,ti. (10912)
- 34 systematic\$ overview\$.ab,sh,ti. (247)
- 35 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (30137)
- 36 exp risk/ (355674)
- 37 odds ratio\$.ab,sh,ti. (39291)
- 38 exp case control study/ (11942)
- 39 exp cohort analysis/ (27460)
- 40 exp longitudinal study/ (11049)
- 41 relative risk\$.ab,sh,ti. (24975)
- 42 case control\$.ab,sh,ti. (30796)
- 43 36 or 37 or 38 or 39 or 40 or 41 or 42 (423533)
- 44 35 and 10 (6)
- 45 43 and 10 (54)
- 46 44 not 24 (0)
- 47 45 not 24 (24)
- 48 from 44 keep 1-6 (6)
- 49 from 24 keep 1-145 (145)
- 50 from 47 keep 1-24 (24)

**DARE**

No. downloaded: 3

Search strategy: as MEDLINE

**HTA**

No. downloaded: 0

**Total refs after deduplication: 448****Parameter searches: quality of life with cirrhosis or HCC****Ovid MEDLINE(R); 1966 to July week 2 2005**

No. retrieved: 28; no. downloaded: 22

- 1 exp Liver Cirrhosis/ (46082)
- 2 exp FIBROSIS/ (9481)
- 3 (cirrhosis adj4 liver\$).tw. (18266)
- 4 1 or 2 or 3 (60679)
- 5 exp Carcinoma, Hepatocellular/ (33497)
- 6 ((hepatocellular adj2 carcinoma\$) or HCC or hepatoma\$).tw. (38681)
- 7 Liver Neoplasms/ (66746)
- 8 5 or 6 or 7 (82628)
- 9 exp fetal proteins/ or exp alpha-fetoproteins/ (13050)
- 10 ((alfa?f?etoprotein\$ or alpha?f?etoprotein\$ or AFP) adj5 (test\$ or exam\$)).tw. (716)
- 11 9 or 10 (13232)
- 12 exp Ultrasonography/ec [Economics] (862)
- 13 LIVER/us [Ultrasonography] (1770)
- 14 ((liver adj5 ultrasound) or (liver adj5 ultrasonograph\$) or LUS).tw. (3145)
- 15 12 or 13 or 14 (5354)
- 16 exp Mass Screening/ (69439)
- 17 (surveillanc\$ or screen\$ or predict\$).ti,ab. (608839)
- 18 16 or 17 (636295)
- 19 11 or 15 or 18 (651886)
- 20 19 and (4 or 8) (11580)
- 21 limit 20 to (humans and english language) (8630)
- 22 value of life/ (4479)
- 23 quality adjusted life year/ (2197)
- 24 quality adjusted life.ti,ab. (1526)
- 25 (qaly\$ or qald\$ or qale\$ or qtime\$).ti,ab. (1192)
- 26 disability adjusted life.ti,ab. (264)
- 27 daly\$.ti,ab. (340)
- 28 health status indicators/ (9256)
- 29 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (4444)
- 30 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (615)
- 31 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab. (508)
- 32 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. (22)
- 33 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab. (252)
- 34 (euroqol or euro qol or eq5d or eq 5d).ti,ab. (614)
- 35 (hql or hqol or h qol or hrqol or hr qol).ti,ab. (1444)
- 36 (hye or hyes).ti,ab. (44)
- 37 health\$ year\$ equivalent\$.ti,ab. (30)
- 38 health utilit\$.ab. (278)
- 39 (hui or hui1 or hui2 or hui3).ti,ab. (307)
- 40 disutil\$.ti,ab. (56)
- 41 rosser.ti,ab. (54)
- 42 quality of well being.ti,ab. (519)
- 43 quality of wellbeing.ti,ab. (2)
- 44 qwb.ti,ab. (95)
- 45 willingness to pay.ti,ab. (600)
- 46 standard gamble\$.ti,ab. (355)
- 47 time trade off.ti,ab. (295)
- 48 time tradeoff.ti,ab. (109)
- 49 tto.ti,ab. (196)
- 50 (index adj2 well being).mp. (1336)
- 51 (quality adj2 well being).mp. (2647)
- 52 (health adj3 utilit\$ ind\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (206)
- 53 ((multiattribute\$ or multi attribute\$) adj3 (health ind\$ or theor\$ or health state\$ or utilit\$ or analys\$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (131)
- 54 quality adjusted life year\$.mp. (2851)
- 55 (15D or 15 dimension\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (414)
- 56 (12D or 12 dimension\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (168)
- 57 rating scale\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (44322)
- 58 linear scal\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (246)
- 59 linear analog\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (622)

- 60 visual analog\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (11628)  
 61 (categor\$ adj2 scal\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (797)  
 62 or/22-61 (83254)  
 63 (letter or editorial or comment).pt. (741291)  
 64 62 not 63 (80758)  
 65 64 and 21 (28)

**EMBASE; 1980 to 2005 week 30**

No. retrieved: 22; no. downloaded: 22

- 1 exp Liver Cirrhosis/ (34380)  
 2 (cirrhosis adj4 liver\$.ti,ab. (13786)  
 3 1 or 2 (37438)  
 4 exp Liver Cell Carcinoma/ (24487)  
 5 ((hepatocellular adj2 carcinoma\$) or HCC or hepatoma\$.ti,ab. (31819)  
 6 Liver Tumors/ (0)  
 7 4 or 5 or 6 (37048)  
 8 alpha fetoproteins/ (9109)  
 9 ((alfa?f?etoprotein\$ or alpha?f?etoprotein\$ or AFP) adj5 (test\$ or exam\$)).ti,ab. (596)  
 10 8 or 9 (9231)  
 11 ((liver adj5 ultrasound) or (liver adj5 ultrasonograph\$) or LUS).ti,ab. (2814)  
 12 exp echography/ (170955)  
 13 11 or 12 (172003)  
 14 exp Mass Screening/ or cancer screening/ (42527)  
 15 (surveillanc\$ or screen\$.ti,ab. (211298)  
 16 14 or 15 (223840)  
 17 (10 or 13) and 16 (9626)  
 18 17 and (3 or 7) (476)  
 19 limit 18 to (humans and english language) (409)  
 20 10 or 13 or 16 (394242)  
 21 20 and (3 or 7) (7387)  
 22 limit 21 to (human and english language) (5683)  
 23 quality adjusted life year/ (2020)  
 24 quality adjusted life.ti,ab. (1492)  
 25 (qaly\$ or qald\$ or qale\$ or qtime\$.ti,ab. (1123)  
 26 disability adjusted life.ti,ab. (243)  
 27 daly\$.ti,ab. (286)  
 28 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (4390)  
 29 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (722)  
 30 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab. (487)  
 31 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. (22)  
 32 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab. (172)  
 33 (euroqol or euro qol or eq5d or eq 5d).ti,ab. (624)  
 34 (hql or hqol or h qol or hrqol or hr qol).ti,ab. (1434)  
 35 (hye or hyes).ti,ab. (25)  
 36 health\$ year\$ equivalent\$.ti,ab. (22)  
 37 health utilit\$.ab. (266)  
 38 (hui or hui1 or hui2 or hui3).ti,ab. (233)  
 39 disutil\$.ti,ab. (62)  
 40 rosser.ti,ab. (44)  
 41 quality of well being.ti,ab. (469)  
 42 quality of wellbeing.ti,ab. (5)  
 43 qwb.ti,ab. (87)  
 44 willingness to pay.ti,ab. (590)  
 45 standard gamble\$.ti,ab. (317)  
 46 time trade off.ti,ab. (297)  
 47 time tradeoff.ti,ab. (104)  
 48 tto.ti,ab. (214)  
 49 (index adj2 well being).mp. (1231)  
 50 (quality adj2 well being).mp. (2445)  
 51 (health adj3 utilit\$ ind\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (201)  
 52 ((multiattribute\$ or multi attribute\$) adj3 (health ind\$ or theor\$ or health state\$ or utilit\$ or analys\$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (126)  
 53 quality adjusted life year\$.mp. (2561)  
 54 (15D or 15 dimension\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (441)  
 55 (12D or 12 dimension\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (156)  
 56 rating scale\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (42132)  
 57 linear scal\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (223)  
 58 linear analog\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (603)



- 59 visual analog\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (13106)
- 60 (categor\$ adj2 scal\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (708)
- 61 or/23-60 (67900)
- 62 (letter or editorial or comment).pt. (433844)
- 63 61 not 62 (66321)
- 64 22 and 63 (22)

### Ovid MEDLINE(R), In-Process & Other Non-Indexed Citations; 26 July 2005

No. retrieved: 1; no. downloaded: 1

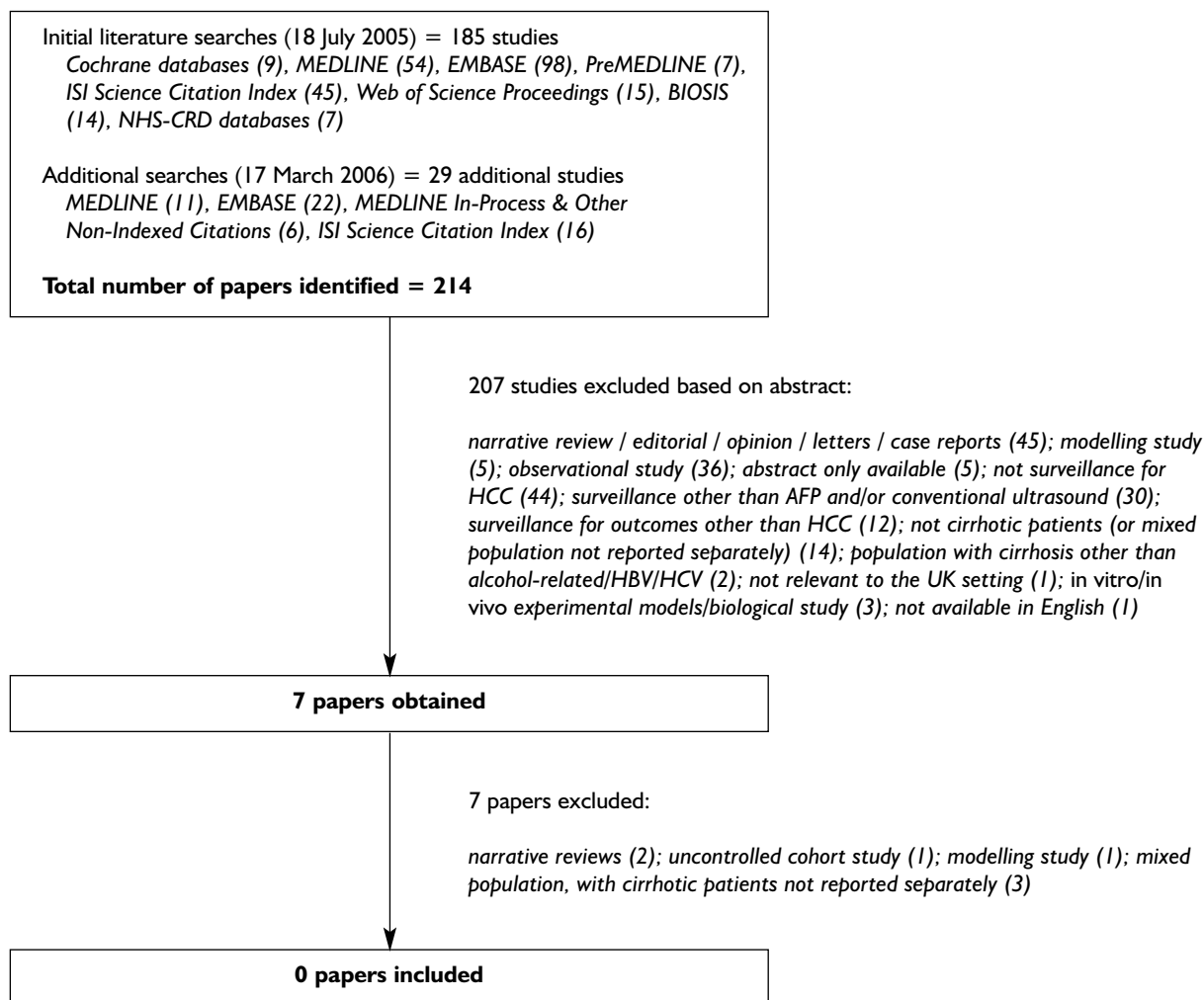
- 1 (cirrhosis adj4 liver\$.tw. (351)
- 2 ((hepatocellular adj2 carcinoma\$) or HCC or hepatoma\$.tw. (935)
- 3 1 or 2 (1182)
- 4 ((alfa?f?etoprotein\$ or alpha?f?etoprotein\$ or AFP) adj5 (test\$ or exam\$)).tw. (8)
- 5 ((liver adj5 ultrasound) or (liver adj5 ultrasonograph\$) or LUS).tw. (70)
- 6 (surveillanc\$ or screen\$ or predict\$.ti,ab. (26667)
- 7 3 or 4 or 5 (1246)
- 8 3 and 7 (1182)
- 9 quality adjusted life.ti,ab. (80)
- 10 (qaly\$ or qald\$ or qale\$ or qtime\$.ti,ab. (75)
- 11 disability adjusted life.ti,ab. (18)
- 12 daly\$.ti,ab. (19)
- 13 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (317)
- 14 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (56)
- 15 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab. (35)
- 16 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. (0)
- 17 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab. (6)
- 18 (euroqol or euro qol or eq5d or eq 5d).ti,ab. (60)
- 19 (hql or hqol or h qol or hrqol or hr qol).ti,ab. (123)
- 20 (hye or hyes).ti,ab. (0)
- 21 health\$ year\$ equivalent\$.ti,ab. (0)
- 22 health utilit\$.ab. (14)
- 23 (hui or hui1 or hui2 or hui3).ti,ab. (21)
- 24 disutil\$.ti,ab. (1)
- 25 rosser.ti,ab. (1)
- 26 quality of well being.ti,ab. (12)
- 27 quality of wellbeing.ti,ab. (0)
- 28 qwb.ti,ab. (0)
- 29 willingness to pay.ti,ab. (36)
- 30 standard gamble\$.ti,ab. (8)
- 31 time trade off.ti,ab. (15)
- 32 time tradeoff.ti,ab. (6)
- 33 tto.ti,ab. (13)
- 34 (index adj2 well being).mp. (49)
- 35 (quality adj2 well being).mp. (111)
- 36 (health adj3 utilit\$ ind\$.mp. [mp=title, original title, abstract, name of substance word] (9)
- 37 ((multiattribute\$ or multi attribute\$) adj3 (health ind\$ or theor\$ or health state\$ or utilit\$ or analys\$)).mp. [mp=title, original title, abstract, name of substance word] (1)
- 38 quality adjusted life year\$.mp. (79)
- 39 (15D or 15 dimension\$.mp. [mp=title, original title, abstract, name of substance word] (29)
- 40 (12D or 12 dimension\$.mp. [mp=title, original title, abstract, name of substance word] (11)
- 41 rating scale\$.mp. [mp=title, original title, abstract, name of substance word] (487)
- 42 linear scal\$.mp. [mp=title, original title, abstract, name of substance word] (76)
- 43 linear analog\$.mp. [mp=title, original title, abstract, name of substance word] (20)
- 44 visual analog\$.mp. [mp=title, original title, abstract, name of substance word] (479)
- 45 (categor\$ adj2 scal\$.mp. [mp=title, original title, abstract, name of substance word] (21)
- 46 or/9-45 (1876)
- 47 (letter or editorial or comment).pt. (17443)
- 48 46 not 47 (1866)
- 49 48 and 8 (1)

**Total refs after deduplication: 38**



## Appendix 3

### Systematic review: identification, retrieval and inclusion/exclusion of studies





## Appendix 4

### Systematic review: studies excluded at full-text stage

Reference	Abstract	Reason for exclusion
Bolondi L. Screening for hepatocellular carcinoma in cirrhosis. <i>J Hepatol</i> 2003;39:1076–1084.	–	Narrative review
Chen JG, Parkin DM, Chen QG, Lu JH, Shen QJ, Zhang BC, et al. Screening for liver cancer: results of a randomised controlled trial in Qidong, China. <i>J Med Screen</i> 2003;10:204–209.	<i>Objectives:</i> To investigate the effectiveness of screening for liver cancer in reducing mortality from the disease in a high-risk population in China. <i>Setting:</i> A randomised controlled trial was carried out among men aged 30–69 who were chronic carriers of hepatitis-B virus (HBsAg positive) during the period 1989–1995 in Qidong county, Jiangsu Province, China. <i>Methods:</i> 5581 HBsAg carriers were identified by population screening and randomly assigned to a screening group (group A, 3712 men), and controls (group B, 1869 men). Screening was planned to be six monthly alpha-fetoprotein (AFP) assays, with follow-up of subjects having an abnormal (greater than or equal to 20 µg/l) test. All subjects were followed up for liver cancer and/or death until 31 December 1995. <i>Results:</i> The overall sensitivity and specificity of the programme was 55.3% and 86.5%, respectively; in subjects who complied with all scheduled screening tests, the values were 80.0% and 80.9%. Three hundred and seventy-four primary liver cancer (PLC) cases were diagnosed. The percentage of cases in stage I was significantly higher in group A (29.6%) than in group B (6.0%). The one-, three-, and five-year relative survival rates were 23.7%, 7.0%, and 4.0% in group A, and 9.7%, 4.0%, and 4.1% in group B respectively, with no difference in five-year survival between the groups. The mortality rate in the screened group (1138 per 100,000 person-years) was not significantly different from that in the controls (1114 per 100,000). A Poisson regression model showed that the probability of death (rate ratio) in the screening group was 0.83 (95% CI 0.68–1.03) relative to the control group. <i>Conclusions:</i> Screening with AFP resulted in earlier diagnosis of liver cancer, but the gain in lead time did not result in any overall reduction in mortality, because therapy for the patients found by screening was ineffective. Further studies using improved methods of screening, diagnosis and treatment are indicated.	Mixed population, with cirrhotic patients not reported separately
Chen VK, Arguedas MR, Fallon MB. Cost-effectiveness of screening strategies for hepatocellular carcinoma in cirrhotics. <i>Hepatology</i> 2001;34:685A.	–	Abstract only; modelling study

continued

Reference	Abstract	Reason for exclusion
Izzo F, Cremona F, Ruffolo F, Palaia R, Parisi V, Curley S. Detection of hepatocellular cancer during screening of 1125 patients with chronic hepatitis virus infection. <i>J Chemother</i> 1997; <b>9</b> :151–2.	–	Uncontrolled cohort study
Saab S. Liver cancer screening in a high-risk population in China fails to reduce mortality. <i>Evid Based Healthcare</i> 2004; <b>8</b> :221–223.	<i>Question:</i> Does liver cancer screening reduce mortality from the disease in a high-risk Chinese population? <i>Study design:</i> Cluster randomised controlled trial. <i>Main results:</i> In people at high risk of liver cancer, screening did not significantly reduce the incidence of primary liver cancer or risk of death compared with no screening (see Table 1), despite earlier detection of the disease (see notes). A table is presented. Per 100,000 person years. <i>Authors' conclusions:</i> Liver cancer screening in a high-risk population in China does not reduce mortality from the disease. © 2004 Elsevier Ltd. All rights reserved.	Review of Chen <i>et al.</i> 2003 (see above)
Yang B, Zhang B, Xu Y, Wang W, Shen Y, Zhang A, <i>et al.</i> Prospective study of early detection for primary liver cancer. <i>J Cancer Res Clin Oncol</i> 1997; <b>123</b> :357–60.	<i>Purpose:</i> To determine whether repeated screening can lead to early detection of primary liver cancer (PLC) and in turn to an improved clinical result. <i>Methods:</i> In this randomised controlled study, Shanghai urban residents aged 35–55 years and with serum evidence of HBV infection or chronic liver disease were eligible for recruitment. Using cluster sampling, these subjects were allocated into two groups – the screening group and the control group: there were 8109 subjects in the screening group and 9711 in the control group. Subjects in the screening group were tested with serum AFP and real-time ultrasound every 6 months. One to four rounds of screening were completed. Liver cancer was treated according to stage at diagnosis. <i>Results:</i> All subjects enrolled were followed up and classed at the end-point as alive without liver cancer, alive with liver cancer, dead from liver cancer, or dead from another cause. The mean follow-up was 1.2 years; total follow-up was 12,038 person-years in the screening group and 9573 person-years in the control group. We detected 38 patients with PLC in the screening group and 18 patients with PLC in the control group. In the patients in the screening group 76.8% of patients were at a subclinical stage, and 70.6% of them underwent resection, the 1- and 2-year survival rates being 88.1% and 77.5%, respectively. However, in the control group, none of the patients was at a subclinical stage when diagnosed, none of them underwent resection, and none of them survived over 1 year. The lead time was estimated at 0.45 years. The cost of detecting PLC at an early stage was RMB 12,600 (US\$1500). <i>Conclusion:</i> The study proved that screening the high-risk population for PLC with a serum AFP test and real-time ultrasound examination can detect patients in the early stages, increase the resection rate and prolong the survival time. It is therefore recommended that screening for PLC be advocated in any high-risk area.	Mixed population, with cirrhotic patients not reported separately

continued

Reference	Abstract	Reason for exclusion
<p>Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. <i>J Cancer Res Clin Oncol</i> 2004; <b>130</b>:417–22.</p>	<p><i>Purpose:</i> Screening for hepatocellular carcinoma (HCC) has been conducted for over 20 years, but there is no conclusive evidence that screening may reduce HCC mortality. The aim of this study was to assess the effect of screening on HCC mortality in people at increased risk. <i>Methods:</i> This study included 18,816 people, aged 35–59 years with hepatitis B virus infection or a history of chronic hepatitis in urban Shanghai, China. Participants were randomly allocated to a screening (9373) or control (9443) group. Controls received no screening and continued to use health-care facilities. Screening group participants were invited to have an AFP test and ultrasonography examination every 6 months. Screening was stopped in December 1997; by that time screening group participants had been offered five to ten times. All participants were followed up until December 1998. The primary outcome measure was HCC mortality. <i>Results:</i> The screened group completed 58.2% of the screening offered. When the screening group was compared to the control group, the number of HCC was 86 versus 67; subclinical HCC being 52 (60.5%) versus 0; small HCC 39 (45.3%) versus 0; resection achieved 40 (46.5%) versus 5 (7.5%); 1-, 3-, and 5-year survival rate 65.9%, 52.6%, 46.4% versus 31.2%, 7.2%, 0, respectively. Thirty-two people died from HCC in the screened group versus 54 in the control group, and the HCC mortality rate was significantly lower in the screened group than in controls, being 83.2/100,000 and 131.5/100,000, respectively, with a mortality rate ratio of 0.63 (95% CI 0.41–0.98). <i>Conclusions:</i> Our finding indicated that biannual screening reduced HCC mortality by 37%</p>	<p>Mixed population, with cirrhotic patients not reported separately</p>





## Appendix 5

### Expert advisory group

The members of the expert advisory group were:

Professor Graeme Alexander (Consultant Hepatologist, Cambridge Transplant Unit, Cambridge University Hospitals NHS Foundation Trust)

Professor Andrew Burroughs (Consultant Hepatologist, Liver Transplant Unit, Royal Free Hospital, London)

Mr Darius Mirza (Consultant Surgeon, The Liver Transplant and Hepatobiliary Unit, Queen Elizabeth Hospital, Birmingham)

Dr John O'Grady (Consultant Hepatologist, Institute of Liver Studies, King's College Hospital, London)

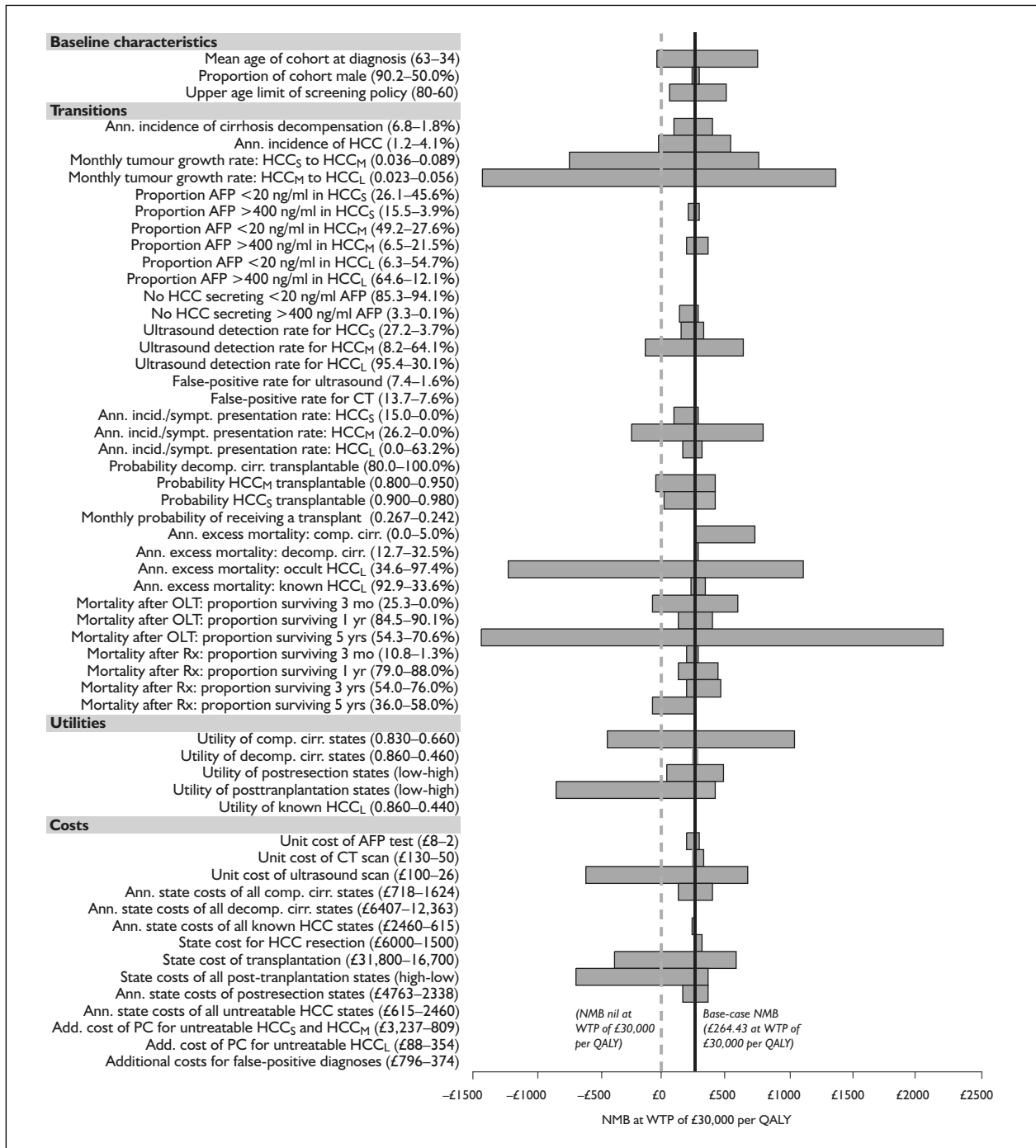
Professor William Rosenberg (Consultant Hepatologist and Facility Director, Wellcome Trust Clinical Research Facility, Southampton General Hospital)

Mr David Stell [Locum Consultant (Liver Surgeon), Derriford Hospital, Plymouth].



# Appendix 6

## One-way sensitivity analyses (net benefit)



**FIGURE 29** One-way sensitivity analysis using net monetary benefit (mixed cohort). Changes in net monetary benefit (NMB) (6-MONTHLY AFP+US vs NO SURVEILLANCE) due to alterations in parameter values over specified ranges (mixed aetiology cohort). Where different ranges were used for different aetiologies, the range shown gives the minimum and maximum value used in any of the three analyses. add., additional; ann., annual; cirr., cirrhosis; comp., compensated; decomp., decompensated; incid./sympt., incidental/symptomatic; PC, palliative care; QALY, quality-adjusted life-year.



## Appendix 7

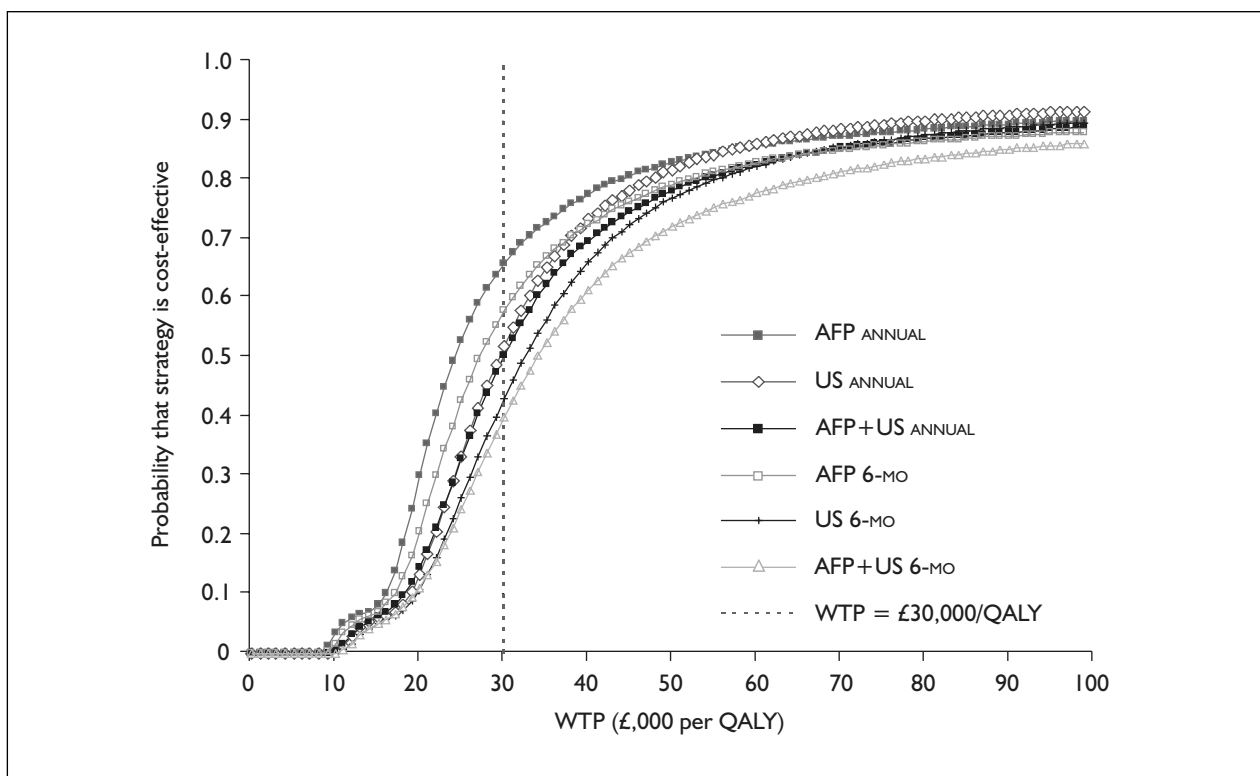
### Comparison of all surveillance strategies with no surveillance

Figures 30–33 show the probability that each surveillance strategy is cost-effective when compared with no surveillance at various maximum WTP thresholds from £10,000 to £100,000 per QALY for the mixed cohort, ALD, HBV and HCV, respectively. These results are based on the results from 10,000 Monte Carlo simulations.

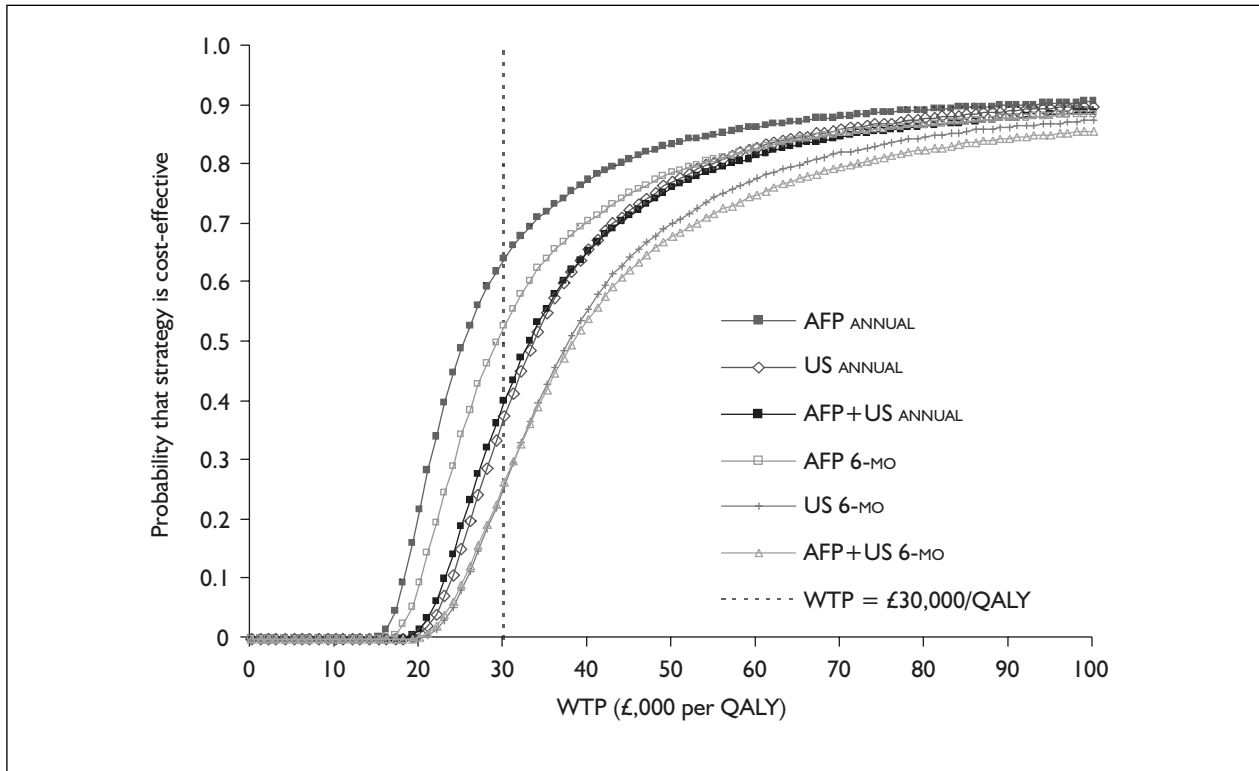
Overall, results for the mixed cohort appear to show that compared with no surveillance, the results for all surveillance strategies are similar. Compared with no surveillance, and with an assumed maximum WTP of £30,000 per QALY, surveillance with annual AFP testing would be considered the most cost-effective. However, the cost-effectiveness of more costly and more effective surveillance strategies should be judged with

reference to the cost-effectiveness acceptability frontiers presented in the selection ‘Relative probability of maximal cost-effectiveness among the surveillance strategies’, p. 78.

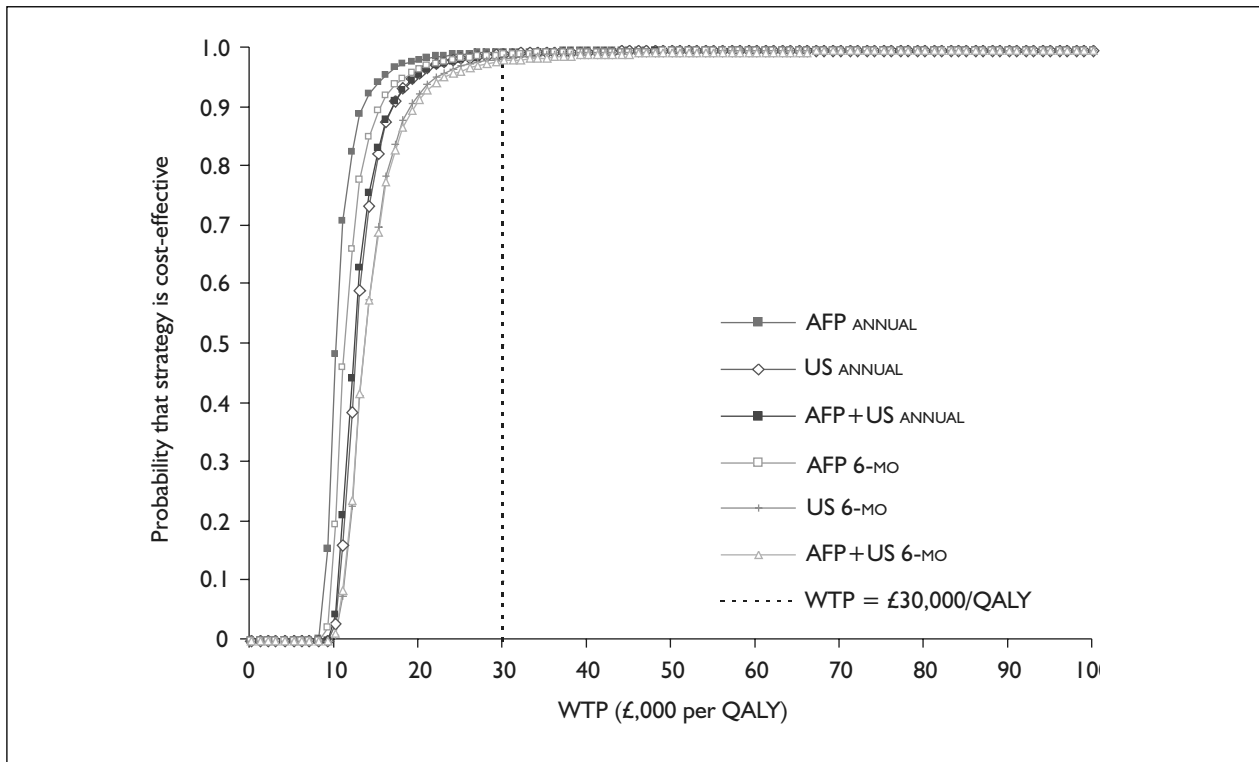
The results for ALD and HBV follow a similar pattern, although one can be confident that all surveillance strategies would be considered cost-effective (when compared with no surveillance) at the £30,000 per QALY level in the HBV cohort. However, in the HCV cohort, compared with NO SURVEILLANCE, surveillance with annual ultrasound appears likely to be the most cost-effective strategy. The reason for the different ranking of results in this cohort is unclear, but could be related to the higher incidence of HCC within this population.



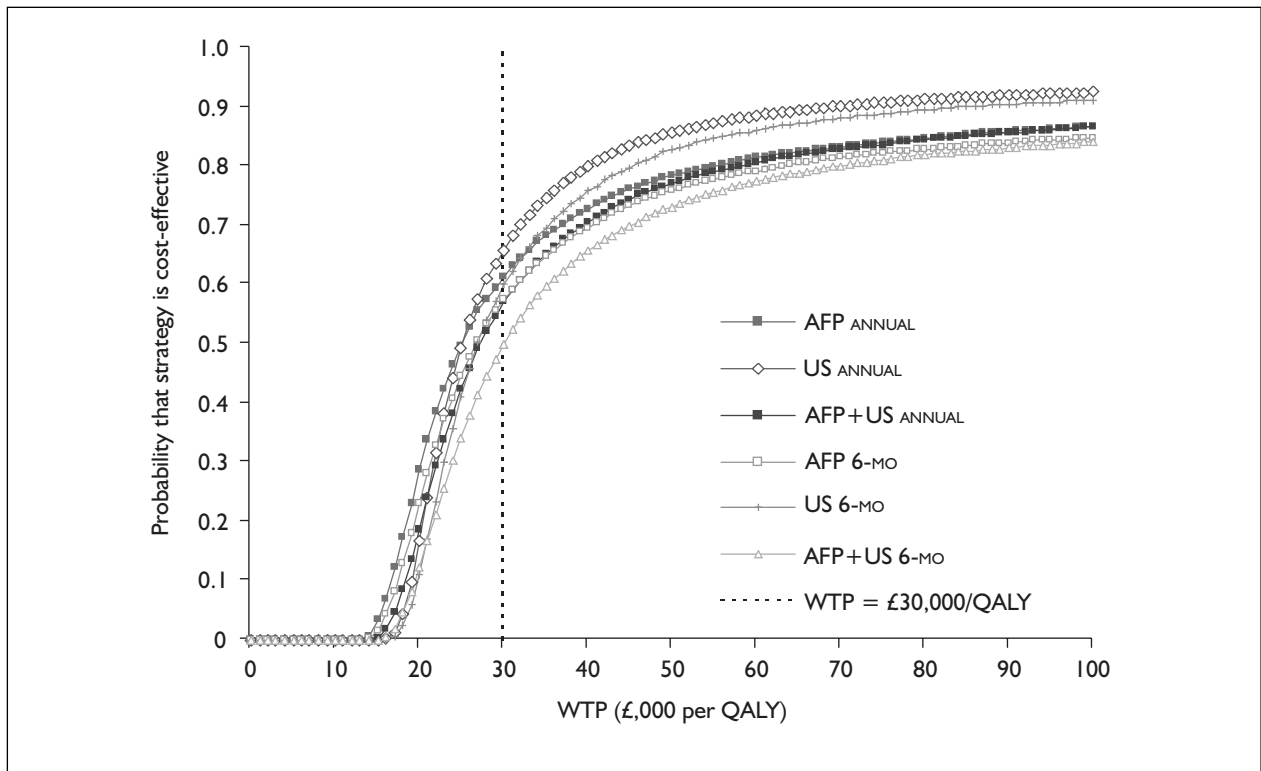
**FIGURE 30** PSA: CEAC for all strategies compared with no surveillance in mixed aetiology cohort. Probability that each surveillance strategy is cost-effective, compared with no surveillance, at WTP thresholds of up to £100,000 per QALY gained. Based on 10,000 Monte Carlo simulations per aetiology, weighted according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV).



**FIGURE 31** PSA: CEAC for all strategies compared with no surveillance in ALD cohort. Probability that each surveillance strategy is cost-effective, compared with no surveillance, at WTP thresholds of up to £100,000 per QALY gained. Based on 10,000 Monte Carlo simulations.



**FIGURE 32** PSA: CEAC for all strategies compared with no surveillance in HBV cohort. Probability that each surveillance strategy is cost-effective, compared with no surveillance, at WTP thresholds of up to £100,000 per QALY gained. Based on 10,000 Monte Carlo simulations.



**FIGURE 33** PSA: CEAC for all strategies compared with no surveillance in HCV cohort. Probability that each surveillance strategy is cost-effective, compared with no surveillance, at WTP thresholds of up to £100,000 per QALY gained. Based on 10,000 Monte Carlo simulations.





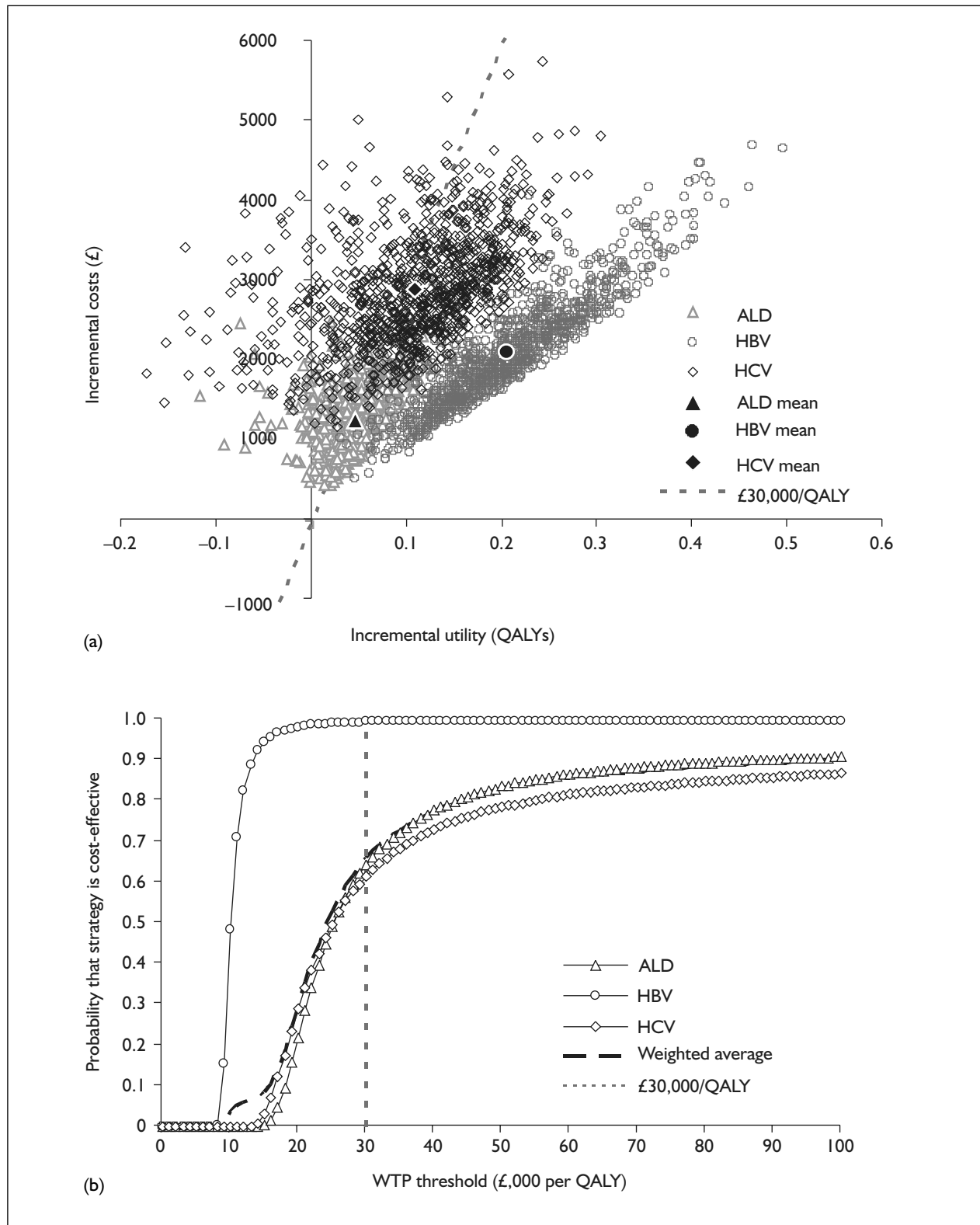
## Appendix 8

### Additional outputs from Monte Carlo simulations

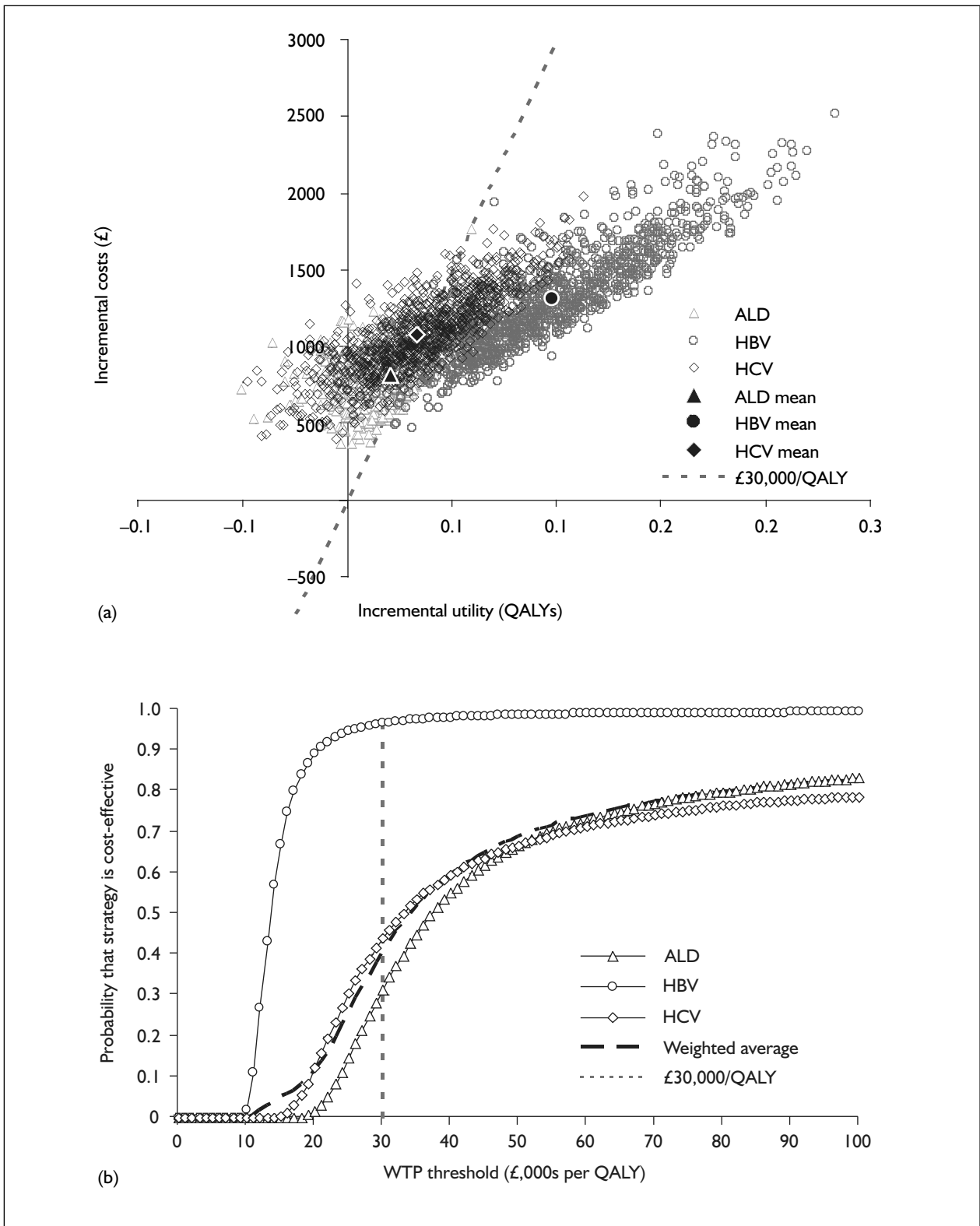
*Figures 34–36* summarise the PSAs for the main surveillance strategy shifts implied by the deterministic cost-effectiveness analysis, for each cirrhosis aetiology and the hypothetical mixed cohort. These are: changing from NO SURVEILLANCE to ANNUAL AFP TRIAGE; changing from ANNUAL AFP TRIAGE to 6-MONTHLY AFP TRIAGE; and changing from 6-MONTHLY AFP TRIAGE to 6-MONTHLY AFP+US.

In order of increasing strategy effectiveness, and if it is assumed that to be acceptable a surveillance strategy must at least have a 50% chance of being cost-effective, then ANNUAL AFP TRIAGE would be chosen regardless of cirrhosis aetiology (and as long as the true WTP for a QALY exceeds

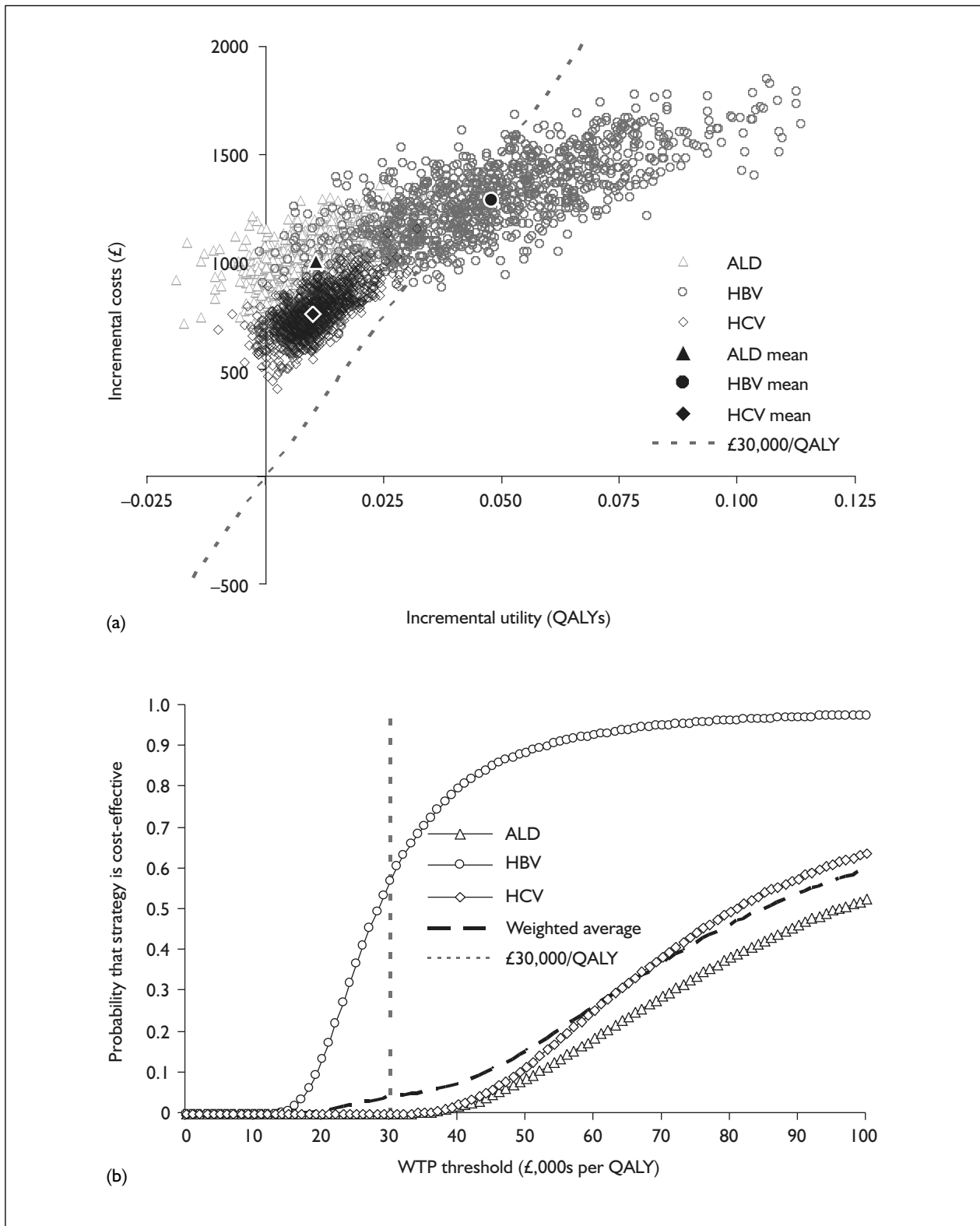
approximately £25,000). However, doubling the frequency of this surveillance strategy to 6-monthly would only be judged cost-effective for those with HBV-related surveillance (although this strategy would still have an approximately 45% chance of being cost-effective for those with HCV-related cirrhosis, at a WTP threshold of £30,000 per QALY). Finally, while surveillance with 6-MONTHLY AFP+US strategy would remain fairly likely to be considered cost-effective for those with HBV-related cirrhosis, this strategy would have a minimal chance of being cost-effective for either HCV- or alcohol-related cirrhosis or for a mixed aetiology cohort (which here comprises a minority of people with HBV-related cirrhosis).



**FIGURE 34** PSA: incremental cost-effectiveness of ANNUAL AFP TRIAGE versus NO SURVEILLANCE. (a) Cost-effectiveness plane showing incremental cost-effectiveness of ANNUAL AFP TRIAGE versus NO SURVEILLANCE in a subsample of 1000 Monte Carlo simulations per aetiology. (b) CEAC showing probability that ANNUAL AFP TRIAGE is cost-effective compared with NO SURVEILLANCE, at WTP thresholds of up to £100,000 per QALY gained. Weighted average calculated according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV). Based on simulation output for 10,000 trials per aetiology.



**FIGURE 35** PSA: incremental cost-effectiveness of 6-MONTHLY AFP TRIAGE versus ANNUAL AFP TRIAGE. (a) Cost-effectiveness plane showing incremental cost-effectiveness of 6-MONTHLY AFP TRIAGE, compared with ANNUAL AFP TRIAGE in a subsample of 1000 Monte Carlo simulations per aetiology. (b) CEAC showing probability that 6-MONTHLY AFP TRIAGE is cost-effective compared with ANNUAL AFP TRIAGE, at WTP thresholds of up to £100,000 per QALY gained; weighted average calculated according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV). Based on simulation output for 10,000 trials per aetiology.



**FIGURE 36** PSA: incremental cost-effectiveness of 6-MONTHLY AFP+US versus 6-MONTHLY AFP TRIAGE. (a) Cost-effectiveness plane showing incremental cost-effectiveness of 6-MONTHLY AFP+US compared with 6-MONTHLY AFP TRIAGE in a subsample of 1000 Monte Carlo simulations per aetiology. (b) CEAC showing probability that 6-MONTHLY AFP+US is cost-effective compared with 6-MONTHLY AFP TRIAGE, at WTP thresholds of up to £100,000 per QALY gained; weighted average calculated according to estimated relative prevalence (57.6% ALD; 7.3% HBV; 35.1% HCV). Based on simulation output for 10,000 trials per aetiology.

## Appendix 9

### Expected value of perfect information results

**TABLE 68** EVPI analysis: per-patient global EVPI in aetiology-specific cohorts (WTP = £30,000 per QALY)

Proposed strategy	Comparator strategy						
	No SURV.	AFP ANNUAL	US ANNUAL	AFP+US ANNUAL	AFP 6-MO	US 6-MO	AFP+US 6-MO
<b>ALD</b>							
NO SURVEILLANCE	–	£320	£122	£181	£354	£122	£156
AFP ANNUAL	£232	–	£1	£0	£64	£1	£10
US ANNUAL	£383	£350	–	£62	£267	£20	£52
AFP+US ANNUAL	£483	£391	£104	–	£225	£1	£16
AFP 6-MO	£459	£257	£111	£28	–	£1	£0
US 6-MO	£763	£731	£401	£340	£537	–	£39
AFP+US 6-MO	£948	£890	£583	£506	£687	£189	–
<b>HBV</b>							
NO SURVEILLANCE	–	£4,023	£3507	£4474	£5637	£4919	£5783
AFP ANNUAL	£6	–	£0	£474	£1620	£937	£1800
US ANNUAL	£8	£518	–	£968	£2132	£1419	£2290
AFP+US ANNUAL	£12	£29	£5	–	£1164	£463	£1329
AFP 6-MO	£13	£12	£6	£2	–	£0	£272
US 6-MO	£18	£53	£18	£24	£725	–	£873
AFP+US 6-MO	£27	£62	£34	£35	£142	£18	–
<b>HCV</b>							
NO SURVEILLANCE	–	£885	£496	£807	£1067	£648	£862
AFP ANNUAL	£665	–	£365	£2	£202	£132	£93
US ANNUAL	£319	£408	–	£343	£601	£168	£431
AFP+US ANNUAL	£815	£231	£529	–	£263	£263	£108
AFP 6-MO	£967	£322	£678	£155	–	£412	£0
US 6-MO	£578	£282	£276	£185	£442	–	£273
AFP+US 6-MO	£1232	£684	£979	£470	£471	£713	–



## Appendix 10

# Individual sampling tumour growth model: methods

### Structure of the model

#### Overview

The population of interest is patients with a diagnosis of compensated cirrhosis (HBV, HCV or alcohol-related), deemed eligible to enter a surveillance programme, i.e. aged 70 years or less with no pre-existing medical conditions that would preclude treatment with transplant or resection (including current alcohol or intravenous drug abuse).

A Monte Carlo simulation model was constructed in which individual differences in tumour growth rate were incorporated into the natural history of HCC. The model was implemented in S-PLUS and R. Comparisons were made between the following surveillance strategies:

- no surveillance
- annual surveillance using AFP alone
- annual surveillance using ultrasound alone
- annual surveillance using AFP and ultrasound
- 6-monthly surveillance using AFP alone
- 6-monthly surveillance using ultrasound alone
- 6-monthly surveillance using AFP and ultrasound.

Technical performance of the testing strategies was modelled using simple decision trees (see *Figure 4*, pp. 24–5). Test sensitivity for ultrasound was varied according to tumour size. Expected costs and utilities were estimated for each surveillance strategy over the patients' life history and used as a basis for comparison. The model structure was developed in collaboration with the expert advisory group and is limited by the availability of reliable and valid parameter estimates against which to calibrate intermediate outputs.

The model runs for the lifetime of the population.

#### Model structure

The natural history model is represented by a five-state continuous time semi-Markov process (*Figure 37*). Surveillance and treatment modules are superimposed onto the natural history model, altering the natural history of the disease process.

#### Simulated populations

A separate variant of the model was developed for each of the three cirrhosis aetiologies (HCV, HBV and alcohol-related). Each variant of the model follows two hypothetical cohorts of people in which different surveillance strategies are used.

The age and gender distribution within the cohorts was based on evidence from appropriate studies in the literature. The size of the cohorts was adjusted according to the magnitude of the Monte Carlo error (with an acceptable error being less than 1% of the relevant parameter). For the base-case analysis, ten cohorts each containing 10,000 individuals were simulated.

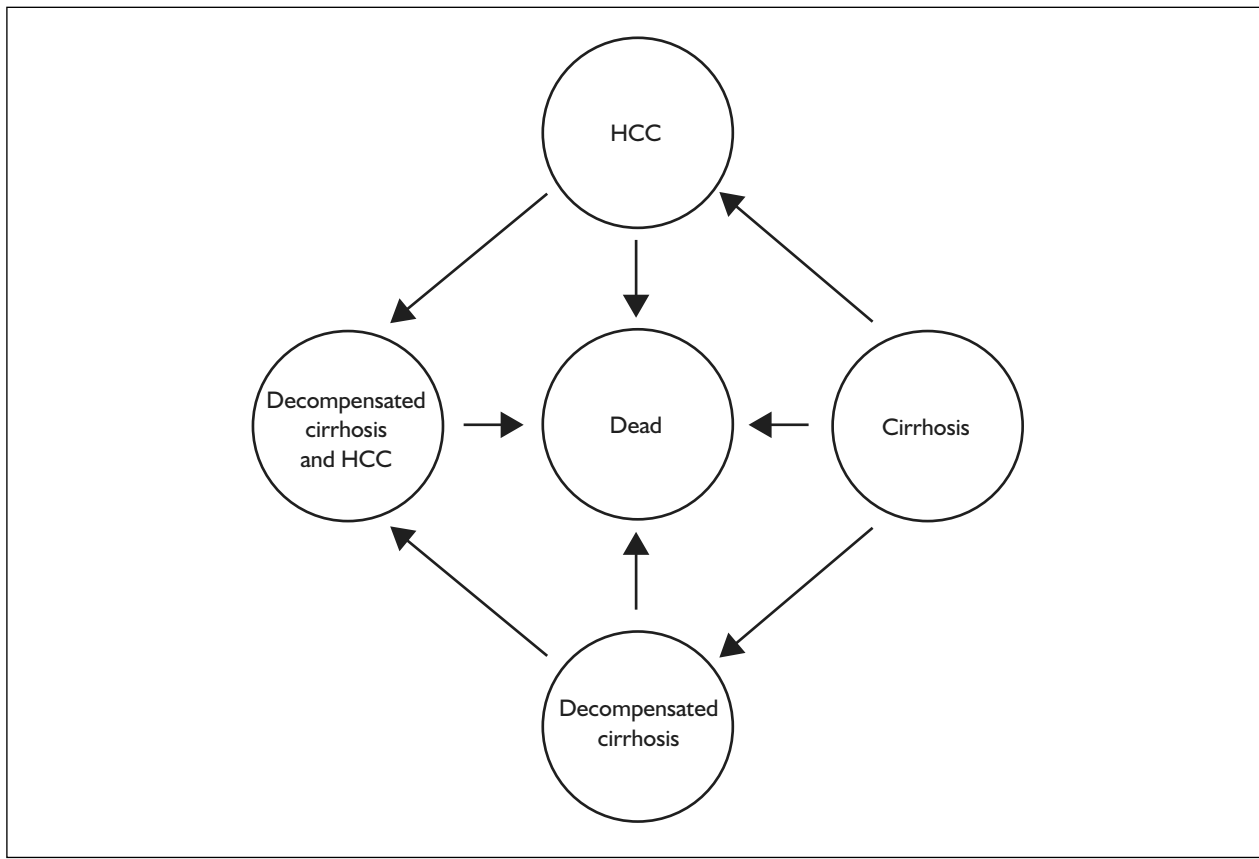
#### Disease process/natural history

The disease process is time dependent and is represented using a five-state continuous time semi-Markov approach (*Figure 37*).

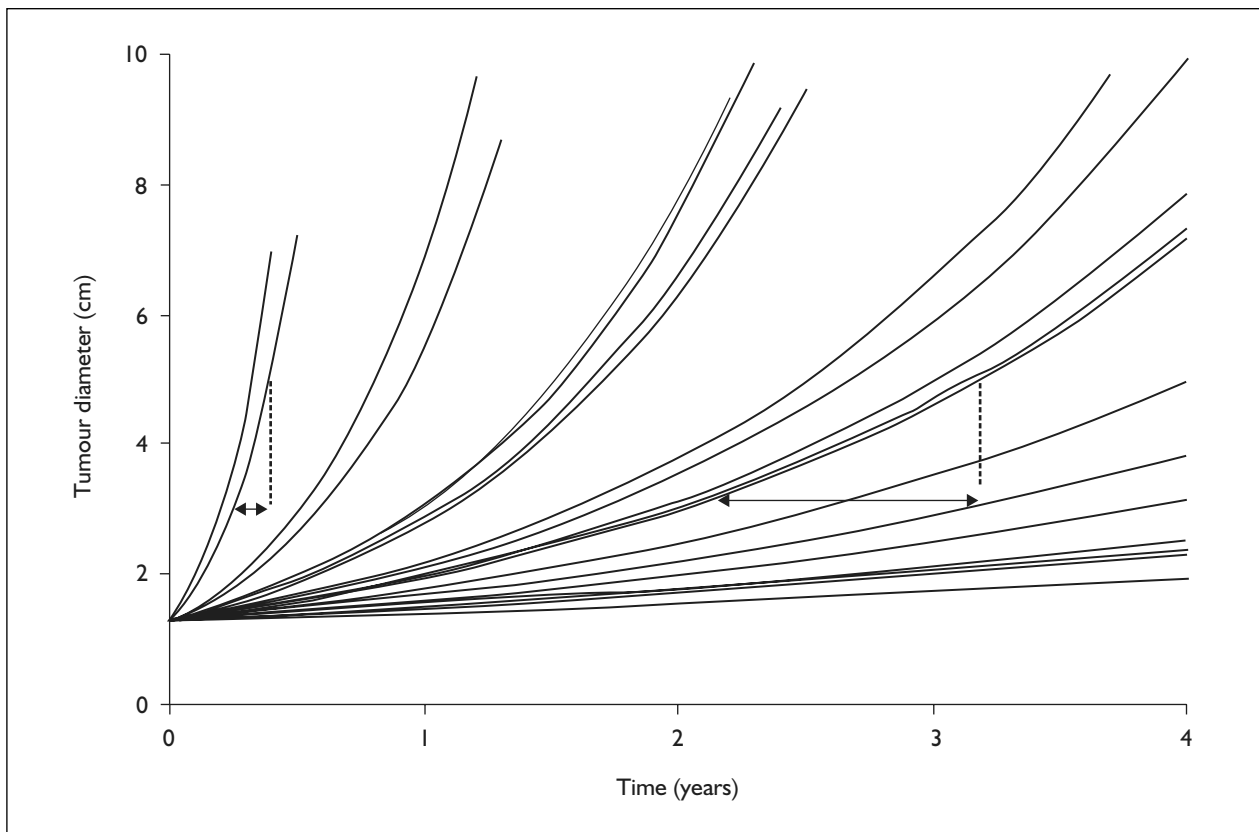
All individuals enter the model with compensated cirrhosis and are exposed to death from background causes according to age- and gender-specific death rates for the reference population. Incidence of decompensation and HCC occurs randomly at aetiology-specific constant rates. The rate of incidence of HCC is the same in compensated and decompensated livers. An aetiology-dependent excess mortality is applied to individuals with decompensated cirrhosis. Similarly, individuals with HCC are subject to an increased risk of death. Owing to the lack of evidence surrounding mortality in patients with a non-symptomatic tumour, the model assumes that the presence of an HCC tumour has no effect on mortality until it reaches a critical size (5 cm), at which point it becomes symptomatic and is associated with an additional mortality rate. Tumour volumes are assumed to grow exponentially. The rate of tumour growth varies from subject to subject according to a log-normal model fitted to individual patient-level data derived from the literature (*Figure 38*).

#### Surveillance programme

Probabilities for the correct and incorrect diagnosis of HCC were calculated according to the appropriate pathways in the testing algorithms.

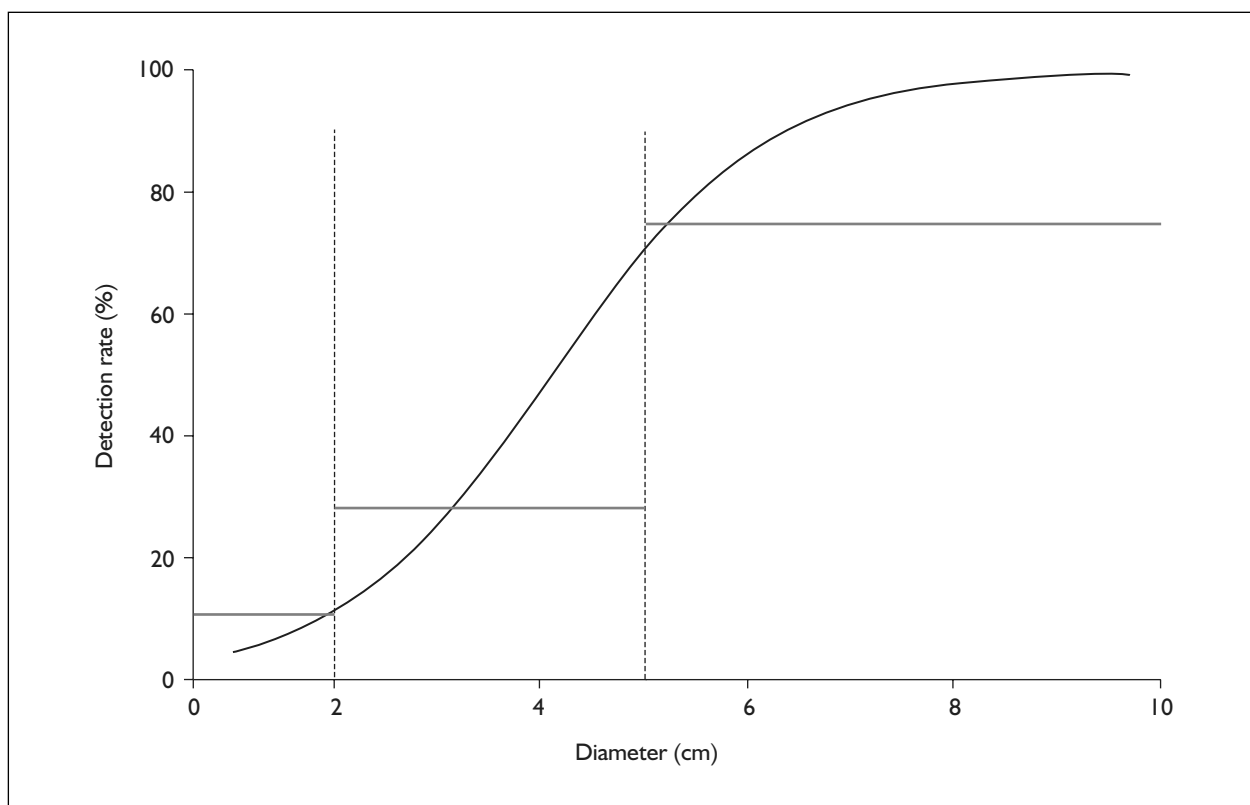


**FIGURE 37** Simulation model: influence diagram



**FIGURE 38** Tumour growth rate





**FIGURE 39** Logistic curve used to define ultrasound test performance

The surveillance programme is applied at 6- or 12-month intervals as appropriate. Other surveillance frequencies were also explored. Test sensitivities were sampled from the distributions shown in *Figures 39* and *40*.

As patients reach the ceiling age for surveillance (70 years old), they leave the surveillance programme and follow a natural history pathway without surveillance.

In the base case, 100% compliance with the surveillance programme was assumed.

Incidental/symptomatic presentation of HCC is permitted for patients with both compensated and decompensated cirrhosis at all stages of disease (e.g. small, medium and large tumours), although with significantly lower probabilities for those with small or medium-sized tumours.

In the base case, all confirmatory imaging is by CT scan.

### Treatment

In the base case, the only treatment option available is liver transplantation. Some patients are deemed unsuitable for surgical treatment,

including those who are diagnosed with a large tumour and those whose tumour becomes large while on the waiting list.

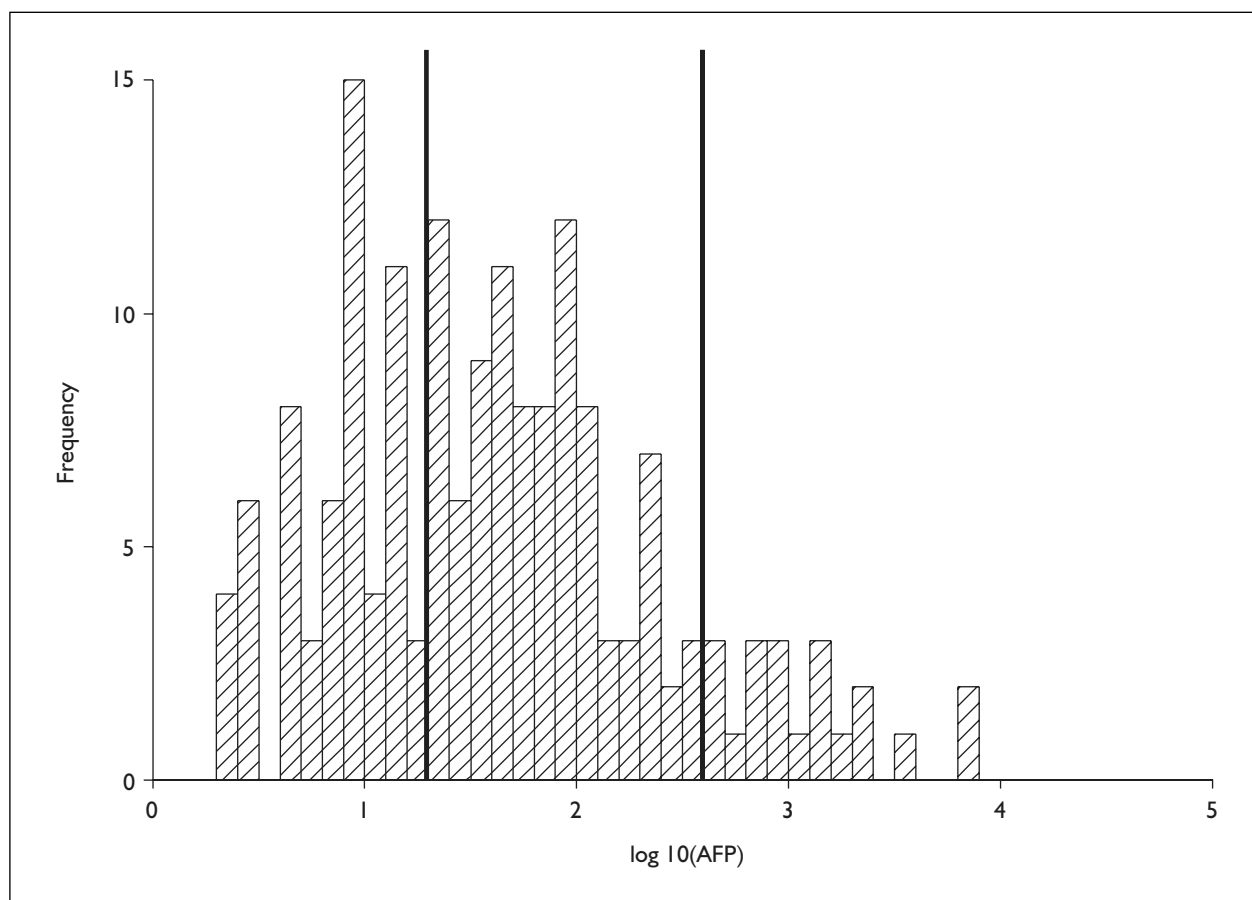
Other treatment options could also be explored.

The numbers of patients who receive transplantation or resection, or who are deemed unsuitable for surgical treatment are based on simple proportions and vary according to tumour size.

Patients can enter the transplant waiting list as a result of diagnosis of HCC or decompensated cirrhosis. Once on the waiting list, patients are subject to the disease process; that is, the tumour can progress from small to medium to large, a decompensated patient without HCC can develop a tumour that may then progress and a compensated patient with a tumour can become decompensated.

There is no prioritisation of patients waiting for a transplant; each patient is as likely to receive a liver as any other, regardless of the reason for listing.

It was assumed that there is no recurrence of HCC post-transplant.



**FIGURE 40** Histogram of AFP in HCC for routine AFP samples. Logarithmic scale; vertical lines correspond to cut-off values of 20 and 400.

Following treatment with transplantation or resection, individuals are subject to excess mortality rates, costs and utilities which encompass a spectrum of post-treatment experiences.

Patients who are deemed to have surgically untreatable HCC (small and medium-sized tumours) enter a series of states (palliative care) which mirror the natural history of the disease. Palliative treatments (radiofrequency thermoablation, percutaneous ethanol injection, transarterial chemoembolisation and best

supportive care) are applied. Once patients progress to 'terminal HCC large', an excess mortality, which reflects the palliation provided by TACE for a proportion of patients, with associated costs and utilities is applied.

#### **Selection of parameters**

A full list of the parameters used in the simulation model appears in *Tables 69–73*. More detailed descriptions of the sources from which these estimates were obtained and a justification of their choice can be found in Chapter 4.

## Baseline characteristics

**TABLE 69** Parameters used in individual sampling tumour growth model: baseline characteristics

Parameter	Cohort	Value	Source	Range of values used in sensitivity analyses	
				Lower	Upper
Mean age of cohort	ALD	53.3	36	43.3	63.3
	HBV	44.0	98	34.0	54.0
	HCV	54.0	64	44.0	64.0
Gender mix of cohort (% male)	ALD	70.1%	ONS	50.0%	90.2%
	HBV	86.5%	98	82.6%	89.7%
	HCV	58.1%	64	53.1%	62.9%
Composition of mixed aetiology cohort	ALD	50%	AA		
	HBV	15%			
	HCV	35%			

## Point estimates

**TABLE 70** Parameters used in individual sampling tumour growth model: point estimates

Parameter	Cohort	Value	Source	Range of values used in sensitivity analyses	
				Lower	Upper
Annual incidence of cirrhosis decompensation	ALD	3.3%	<sup>a</sup>	1.8%	7.0%
	HBV	3.3%	67	1.8%	6.0%
	HCV	5.3%	67	3.9%	7.0%
Annual incidence of HCC	ALD	1.7%	323	1.2%	2.2%
	HBV	2.2%	323	1.6%	2.8%
	HCV	3.7%	323	3.2%	4.2%
Probability of AFP <20 ng/ml in patients with no HCC	All	0.906	251	0.853	0.941
Probability of AFP 20–400 ng/ml in patients with no HCC	All	0.088	251	0.054	0.140
Probability of AFP >400 ng/ml in patients with no HCC	All	0.006	251	0.001	0.033
False-positive rate for ultrasound	All	3.5%	256	1.6%	7.4%
Probability of detection of HCC by CT	All	1.000	AA	0.605	
False-positive rate for CT	All	0.898	325	7.6%	13.7%
Proportion with decompensated cirrhosis who are listed for OLT	All	100%	AA	80%	100%
Proportion with HCC <5 cm who are listed for OLT on detection	All	90%	AA	80%	95%
Proportion with HCC <5 cm who receive resection on detection	All	0%	AA	<sup>b</sup>	<sup>b</sup>
90-day mortality rate for patients undergoing OLT	ALD	6.0%	UKT	0.0%	12.6%
	HBV	15.0%		4.7%	25.3%
	HCV	7.4%		3.0%	11.8%
Proportion of patients surviving 1 year following OLT	ALD	92.0%	UKT	84.5%	99.5%
	HBV	78.0%		65.9%	90.1%
	HCV	87.6%		81.9%	93.3%
Proportion of patients surviving 5 years following OLT	ALD	54.7%	UKT	38.2%	71.3%
	HBV	68.5%		54.3%	82.8%
	HCV	55.8%		41.0%	70.6%

continued

**TABLE 70** Parameters used in individual sampling tumour growth model: point estimates (cont'd)

Parameter	Cohort	Value	Source	Range of values used in sensitivity analyses	
				Lower	Upper
Annual mortality rate due to decompensated cirrhosis	ALD	17.7%	<sup>c</sup>	12.7%	32.5%
	HBV	22.5%	67	18.9%	32.5%
	HCV	12.9%	64	12.7%	14.0%
Annual mortality rate due to compensated cirrhosis	All	0%	AA	0%	5%
Annual mortality rate due to HCC >5 cm	All	91.0%	ONS <sup>109</sup>		
90-day mortality rate for patients undergoing resection	All	3.9%	216	1.3%	10.8%
Proportion of patients surviving 1 year following resection	All	85.0%	216	79.0%	88.0%
Proportion of patients surviving 3 years following resection	All	62.0%	216	54.0%	76.0%
Proportion of patients surviving 5 years following resection	All	51.0%	216	36.0%	

<sup>a</sup> Assumed same as HBV in absence of a reliable ALD-specific estimate.  
<sup>b</sup> Strategies including resection examined in scenario analyses.  
<sup>c</sup> Average of HBV and HCV values in absence of a reliable ALD-specific estimate.

**TABLE 71** Parameters used in individual sampling tumour growth model: data sets

Parameter	Source	Method of implementation
Tumour growth rate	324	Random tumour growth rates assuming exponential growth according to a Gaussian distribution, fitted to reported individual patient-level data
Probability of detection of HCC by AFP	10,287,293,326–328	AFP levels sampled from distribution extracted from individual patient-level data and compared with threshold
Probability of detection of HCC by ultrasound	256	Detection rate a function of tumour diameter according to a logistic curve, fitted to reported point-estimates of ultrasound sensitivity for different tumour sizes
Probability of symptomatic/incidental presentation of HCC	278	Presentation rate proportional to tumour diameter, with exponential function calibrated to reported rates of symptomatic/incidental presentation
Time on OLT waiting list <sup>a</sup>	UKT	Waiting times sampled from distribution

<sup>a</sup> All patients have the same probability of receiving a transplant, regardless of reason for listing.

## Resource use and costs

**TABLE 72** Parameters used in individual sampling tumour growth model: values affecting costs

Parameter	Value	Range of values used in sensitivity analyses	
		Lower	Upper
<b>Unit costs</b>			
AFP test	£4 per test	£2	£8
CT scan	£110 per scan	£50	£130
Ultrasound scan	£50 per scan	£26	£100
MRI scan	£200 per scan	£180	£400
Outpatient appointment	£101 per appointment	£72	£133
PEI	£754 per procedure	£377	£1,508
RFA	£381 per procedure	£190	£762
TACE	£537 per procedure	£268	£1,074
<b>State costs</b>			
All compensated cirrhosis states	£1,171 per year	£718	£1,624
All decompensated cirrhosis states	£9,385 per year	£6,407	£12,363
All known HCC states	£1,230 extra <sup>a</sup> per year	£615	£2,460
OLT	£21,800 per operation	£16,700	£31,800
Post-OLT (year 1)	£9,872 per patient per year	£4,831	£14,921
Post-OLT (year 2 onwards)	£1,564 per patient per year	£821	£2,315
Resection	£5,400 per operation	£1,500	£6,000
Postresection	£3,532 per patient per year	£2,338	£4,763
Palliative care (HCC <sub>S</sub> and HCC <sub>M</sub> )	£1,619 extra <sup>b</sup> per year	£809	£3,237
Palliative care (HCC <sub>L</sub> )	£177 extra <sup>b</sup> per year	£88	£354
<b>Event costs</b>			
False-positive diagnosis	£512 per false-positive diagnosis	£374	£796
Symptomatic/incidental diagnosis	£164 per diagnosis	£78	£238

<sup>a</sup> In addition to costs of underlying cirrhosis.  
<sup>b</sup> In addition to costs of underlying cirrhosis and costs of HCC.

## Utilities

**TABLE 73** Parameters used in individual sampling tumour growth model: utilities

Health state	Markov states applied to	Value	Source	Range of values used in sensitivity analyses	
				Lower	Upper
Compensated cirrhosis	All compensated cirrhosis states ( $\pm$ known or occult HCC <sub>S</sub> or HCC <sub>M</sub> , including patients on the OLT waiting list)	0.75	312	0.66	0.83
Decompensated cirrhosis	All decompensated cirrhosis states ( $\pm$ known or occult HCC <sub>S</sub> or HCC <sub>M</sub> , including patients on the OLT waiting list)	0.66	312	0.46	0.86
HCC	Terminal HCC <sub>L</sub>	0.64	312	0.44	0.86
Post-OLT (year 1)	Post-OLT (year 1)	0.69	318	0.64	0.74
Post-OLT (year 2+)	Post-OLT (year 2 onwards)	0.73	318	0.67	0.78
Postresection	Postresection (survivors)	0.73	<sup>a</sup>	0.62	0.84

<sup>a</sup> Weighted average of values adopted for compensated and decompensated cirrhosis, calculated to approximate average clinical course



## Appendix II

### Comparison of present study with other published cost-effectiveness analyses

**TABLE 74** Comparison of present study with other published cost-effectiveness analyses: design

	PenTAG (HCV)	Arguedas <sup>304</sup>	Lin <sup>306</sup>	Patel <sup>307</sup>
Initial age of cohort	54	50	40	45
Initial disease status of cohort	HCV-related compensated cirrhosis	HCV-related compensated (80%) and decompensated (20%) cirrhosis	HCV-related compensated cirrhosis	HCV-related compensated cirrhosis
Stopping criterion: model stopped	All dead	After 50 years, or all dead	Not stated	Until age 80 (i.e. 40 years) or dead
Cycle length	1 month	6 months	1 month	6 months
Comparison with no surveillance	Yes	Yes	Yes	Yes
Comparison with 6-monthly AFP and US	Yes	No (policy in which AFP and US are alternated 6-monthly is considered)	Yes, and screening stops at age 70	Yes
Comparison with annual AFP and US	Yes	No	Yes, and screening stops at age 70	No
Sensitivity of AFP with US	0.178 (HCC <sub>S</sub> ) 0.373 (HCC <sub>M</sub> ) 0.833 (HCC <sub>L</sub> )	NA	0.85	0.79
Specificity of AFP with US	0.965	NA	0.8	0.87
Distinction between different tumour sizes?	Yes: Small <2 cm Medium 2–5 cm Large >5 cm	Yes: Small <5 cm Large >5 cm, (or multifocal or complicated by PVT)	Yes: Resectable Unresectable	Yes: Small <2 cm Medium 2–5 cm Large >5 cm
Distinction between known and unknown (or occult) HCC	Yes	No <sup>a</sup>	Yes	Yes
Rate of incidence of HCC?	Constant (same value regardless of stage of cirrhosis)	Increases with onset of decompensation	Increases with duration of cirrhosis and increased incidence postresection	Constant (same value regardless of stage of cirrhosis)
Allowance of incidental/symptomatic diagnosis of HCC?	Yes	Yes, with symptoms	Yes, but may be in no screening arm only	Only when large (>5 cm)
Excess mortality is associated with:	Large HCC (known and unknown), decompensated cirrhosis, post-transplant and postresection	Large HCC, various acute complications and resection	Compensated and decompensated cirrhosis, unresectable tumours	Compensated and decompensated cirrhosis, untreatable HCC, post-transplant and postresection

*continued*

**TABLE 74** Comparison of present study with other published cost-effectiveness analyses: design (cont'd)

	<b>PenTAG (HCV)</b>	<b>Arguedas<sup>304</sup></b>	<b>Lin<sup>306</sup></b>	<b>Patel<sup>307</sup></b>
Treatment of acute complications	Not separately modelled	Modelled separately; both a distinct possible pathway to decompensation, and acute events for those already decompensated	Not separately modelled	No
Treatment for decompensation (without HCC)?	Liver transplant	Liver transplant	Assume liver transplant, but not clearly stated	Liver transplant (cadaveric or living donor)
Treatment for HCC	Mixture of resection and transplant (in base case analysis); possibility of all getting transplant (no resection) modelled as a scenario analysis; palliative care for all large tumours	80% resection (small HCCs in comp. cirrh.) 80% CE/RFA (small tumours in decomp. cirrh.) followed by transplant; palliative care for all large tumours	Resection only for those resectable; palliative treatment for all others; 100% compliance (some transplant as sensitivity analysis)	Liver transplant
Are untreatable tumours modelled?	Yes	Yes, 20% of small HCCs; also, annual probability of getting OLT = 31%	Yes, unresectable tumours get palliative care	Yes, receive palliative care
Possibility of incidental/symptomatic diagnosis in the no surveillance protocol?	Yes	Symptomatic diagnosis of large HCCs only Rate? 100%?	Yes	Yes, symptomatic presentation only of large HCC tumours
Possibility of postresection HCC recurrence	No (but have postresection-specific excess mortality)	Yes, treated by OLT	Yes (0.02–0.1 annual incidence dependent on duration of cirrhosis)	Yes, reflected in postresection all-cause mortality
Costs included	Test costs (AFP, US, CT, MRI); procedure costs (resection and transplantation); ongoing care costs (comp. cirrhosis, decomp. cirrhosis, post-transplantation, postresection, palliative care)	Test costs; resection/transplantation CE/RFA; outpatient costs for acute complications; terminal care for HCC; outpatient visits and therapies	Test costs (AFP, US, triphasic CT, angiography, preoperative tests); procedures: resection, transplantation, biopsy, TACE, PEI; cirrhosis-related outpatient care; cancer-related terminal care	Test costs (AFP, US CT); care costs (comp. cirrhosis, decomp. cirrhosis, untreatable HCC); procedures: resection, transplantation Post-transplantation and postresection care

<sup>a</sup> Probability of HCC being small at diagnosis appears to be the same with and without screening; however, all small tumours are asymptomatic (and therefore only found by screening).  
CE, chemoembolisation; PVT, portal venous thrombosis.





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### **Feedback**

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***We look forward to hearing from you.***