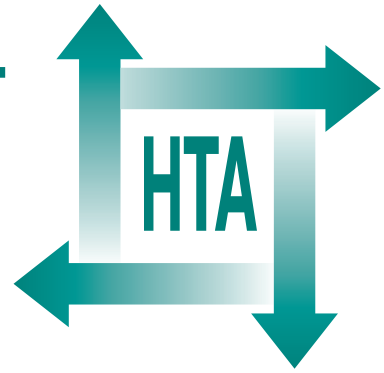
Health Technology Assessment 2006; Vol. 10: No. 32

The cost-effectiveness of testing for hepatitis C in former injecting drug users

E Castelnuovo, J Thompson-Coon, M Pitt,
M Cramp, U Siebert, A Price and K Stein

September 2006

Health Technology Assessment
NHS R&D HTA Programme



How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

The cost-effectiveness of testing for hepatitis C in former injecting drug users

E Castelnuovo,[1] J Thompson-Coon,[1] M Pitt,[1] M Cramp,[2] U Siebert,[3] A Price[4] and K Stein[1*]

[1] Peninsular Technology Assessment Group, Peninsular Medical School, Universities of Exeter and Plymouth, UK
[2] Derriford Hospital, Plymouth, UK
[3] Institute for Technology Assessment, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[4] Southampton Health Technology Assessment Group, UK

* Corresponding author

Declared competing interests of authors: K Stein received an unrestricted grant from Schering Plough (UK) to carry out work on the cost-effectiveness of combination therapy for hepatitis C in 2000. KS is a member of the editorial board of *Health Technology Assessment*, but he was not involved in the editorial process for this report. M Cramp sits on hepatitis C advisory boards for both Schering Plough and Roche. He has received unrestricted educational grants from Roche and Schering Plough to support research and service development. He has been awarded an NHS R&D grant looking at injecting drug users who do not have hepatitis C virus infection. U Siebert has received an HTA grant from the German Agency of Health Technology Assessment at the German Institute for Medical Documentation and Information/German Federal Ministry of Health and Social Security and unrestricted research grants from ESSEX Pharma GmbH, Munich, Germany (German subsidiary of Schering Plough Inc., Kenilworth, NJ, USA). J Thompson-Coon received a grant from The Hepatitis C Trust to conduct a systematic review of complementary and alternative therapies for the treatment of chronic hepatitis C.

Published September 2006

This report should be referenced as follows:

Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, *et al*. The cost-effectiveness of testing for hepatitis C in former injecting drug users. *Health Technol Assess* 2006;**10**(32).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®*/Clinical Medicine.

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a short time period.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned by the HTA Programme as project number 04/40/01. The contractual start date was in November 2004. The draft report began editorial review in June 2005 and was accepted for publication in September 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

Abstract

The cost-effectiveness of testing for hepatitis C in former injecting drug users

E Castelnuovo,[1] J Thompson-Coon,[1] M Pitt,[1] M Cramp,[2] U Siebert,[3] A Price[4] and K Stein[1*]

[1] Peninsular Technology Assessment Group, Peninsular Medical School, Universities of Exeter and Plymouth, UK
[2] Derriford Hospital, Plymouth, UK
[3] Institute for Technology Assessment, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[4] Southampton Health Technology Assessment Group, UK
* Corresponding author

Objectives: To evaluate the effectiveness and cost-effectiveness of testing for hepatitis C (HCV) among former injecting drug users (IDUs).
Data sources: Electronic databases 1996–October 2004. Trent Regional Database Study. Routine UK mortality data.
Review methods: A decision analytic model was developed to investigate the impact of case-finding and treatment on progression of HCV disease in a hypothetical cohort of 1000 people. This was compared with a cohort in whom no systematic case-finding is implemented but spontaneous presentation for testing is allowed to occur. A group of epidemiological and clinical experts informed the structure of the model, which has three main components: (1) testing and diagnosis, (2) treatment, and (3) long-term consequences of infection. A fourth component, case-finding strategies, examines the potential impact of case-finding in three settings: prisons, general practice and drug services.
Results: Case-finding for HCV is likely to prevent, for 1000 people approached, three cases of decompensated cirrhosis, three deaths due to HCV and one case of hepatocellular cancer (at 30 years). Twenty-five additional people are likely to undergo combination therapy as a result of initial case-finding. One liver transplant is likely to be prevented for 10,000 people included in case-finding. Case-finding is likely to cost, in the general case, around £760,000 more than a policy of not case-finding. The total cost of either strategy is high and driven predominantly by the cost of treatment with combination therapy (the costs of long-term consequences are heavily discounted owing to the duration of the model). Systematically offering testing to 1000 people would cost around £70,000. In terms of life-years gained, case-finding is likely to result in an additional life-year gained for an investment of £20,084. Taking impacts on quality of life into account gives an estimate for the cost–utility of case-finding as £16,514 per QALY. The probabilistic sensitivity analysis shows that, if NHS policy makers view £30,000 per QALY as an acceptable return on investment, there is a 74% probability that case-finding for HCV would be considered cost-effective. At £20,000 per QALY, the probability that case-finding would be considered cost-effective is 64%. In all analyses, the probability of case-finding being considered cost-effective at a level of £30,000 per QALY was high. Case-finding in drug services is likely to be the most expensive, owing to the high prevalence of cases in the tested population. Correspondingly, benefits are highest for this strategy and cost-effectiveness is similar, in average terms, to the general case. Case-finding in general practice by offering testing to the whole population aged 30–54 years is, paradoxically, estimated to be the least expensive option as only a small number of people accept the offer of testing and HCV prevalence in this group is much higher than would be expected from the general population. Two approaches to case-finding in prison were considered, based on the results of studies in Dartmoor and the Isle of Wight prisons. These differed substantially in the prevalence of cases identified in the tested populations. The analysis based on data from Dartmoor prison had the least favourable average cost-effectiveness of the strategies considered (£20,000 per QALY). Subgroup analyses based on duration of infection show that case-finding is likely to be most cost-effective in people whose infection is more long-standing and who are consequently at greater risk of progression. In people

who were infected more than 20 years previously, case-finding yields benefits at around £15,000 per QALY. Treatment effectiveness was modelled using estimates from randomised controlled trials and lower rates of viral response may be seen in practice. However, estimates of cost-effectiveness remained below £30,000 for all levels of treatment effectiveness above 58% of those shown in the relevant trials. The value of information analysis, based on assumptions that 10,000 people might be eligible for case-finding and that programmes would run for 15 years, suggests that the maximum value of further research into case-finding is in excess of £19 million. Partial expected value of perfect information (EVPI) analysis shows that the utility estimates used in the model eclipse all other factors in terms of importance to parameter uncertainty. This is not surprising, since the point estimates for differences in utility between states and across the arms of the model are small.

Conclusions: Case-finding for hepatitis C is likely to be considered cost-effective by NHS commissioners. Although there remains considerable uncertainty, it appears unlikely that cost-effectiveness would exceed the levels considered acceptable. Further improvements in the effectiveness of treatments to slow or halt disease progression are likely to improve the cost-effectiveness of case-finding. Case-finding is likely to be most cost-effective if targeted at people whose HCV disease is probably more advanced. Further empirical work is required to specify, in practice, different approaches to case-finding in appropriate settings and to evaluate their effectiveness and cost-effectiveness directly.

Contents

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

Encephalopathy Confusion and forgetfulness caused by poor liver function and the diversion of blood flow away from the liver

Enzyme-linked immunosorbent assay A test used to identify antibodies to hepatitis C virus

Fibrosis The formation of fibrous or scar tissue which occurs as a result of viral hepatitis

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

Histopathology Activity Index (HAI) score A grading system for assessing histological activity in chronic hepatitis

Injecting drug user A drug user who misuses drugs by injection, regardless of the route of injection (subcutaneous, intramuscular or intravenous)

Ishak score A numerical scoring system for assessing histological activity in chronic hepatitis

Knodell score A numerical scoring system for assessing histological activity in chronic hepatitis

Metavir A numerical scoring system for assessing histological activity in chronic hepatitis

Polymerase chain reaction A test used to identify hepatitis C RNA, that is, the presence of viral particles

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

Sustained virological response Clearance of hepatitis C virus RNA, which is maintained for at least 24 weeks after cessation of treatment (<100 copies/ml)

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

ALT	alanine aminotransferase
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
ELISA	enzyme-linked immunosorbent assay
EVPI	expected value of perfect information
GUM	genitourinary medicine
HAI	Histological Activity Index
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICER	incremental cost-effectiveness ratio
IDU	injecting drug user
IFN	interferon
LYG	life-year gained
NICE	National Institute for Health and Clinical Excellence
PCR	polymerase chain reaction
PegIFN	pegylated interferon
pEVPI	partial expected value of perfect information
PSA	probabilistic sensitivity analysis
PSSRU	Personal and Social Services Research Unit
QALY	quality-adjusted life-years
QoL	quality of life
RCT	randomised controlled trial
RIBA	recombinant immunoblot assay
RNA	ribonucleic acid
SF-36	Short Form with 36 items
SVR	sustained viral response
TAR	Technology Assessment Report
WHO	World Health Organization

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

Objective

The objective of this assessment was to evaluate the effectiveness and cost-effectiveness of testing for hepatitis C virus (HCV) among former injecting drug users (IDUs).

Description of proposed service

Testing is defined as efforts to identify people with HCV infection and to offer them antibody and, if necessary, RNA testing, that is, systematic case-finding.

Case-finding for HCV may take place in a range of settings, using a variety of methods. This assessment examines a general case of systematic case-finding and explores the effectiveness and cost-effectiveness of case-finding in specific settings using a range of approaches: general practice, prisons and services for people who misuse drugs and alcohol. The population of interest is people who are former IDUs. In most, although not all, settings considered, the initial step in case-finding is the identification of this population group. In addition, two scenarios are considered in which testing is offered to whole populations: prison inmates and, according to age, people in contact with general practices.

HCV status is investigated using enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) testing. People with chronic HCV infection are considered for combination therapy using pegylated interferon and ribavirin in standard doses for 48 weeks. Treatment is offered without histological staging to people who are otherwise eligible and whose HCV infection is with genotypes 2 and 3. People with other genotypes (predominantly 1 and 4) are offered biopsy to assess the severity of liver damage. Cases with moderate to severe hepatitis are offered treatment, if otherwise eligible. Cases of mild hepatitis with genotypes 1 and 4 undergo monitoring, with subsequent treatment if the severity of hepatitis advances.

In order to consider potential benefits of case-finding other than antiviral combination therapy, the impact of offering brief interventions aimed at reducing the incidence of alcohol intake above prescribed limits is also examined.

Epidemiology and background

Hepatitis C is a blood-borne RNA virus which causes slowly progressive chronic liver disease. The most common viral genotypes in England are 1a (32%), 1b (15%) and 3a (37%). The virus is transmitted primarily as a result of contact with blood and blood products. Sharing of injecting paraphernalia among IDUs is currently the commonest route for infection. Sexual and vertical transmission may occur but are unusual.

Approximately 80% of people exposed to HCV will fail to clear the virus during the acute phase and will become chronically infected. Acute infection is usually asymptomatic. Chronic symptoms are non-specific and, in general, mild until progression of liver disease occurs.

The prevalence of HCV is thought to be around 0.4% in England and Wales. The majority of known cases in 2003 were aged <45 years old. A cohort study among new IDUs in London and Brighton (2001) suggests a high prevalence and rising incidence of HCV infection. The incidence of chronic infection in IDUs is around 40%, although some regional variation (33–57%) has been shown. The prevalence of former IDUs is uncertain and available estimates of 0.22–0.8% of the general population may underestimate the size of this population.

HCV infection impacts on quality of life, demonstrated using a wide range of health status measures. Fatigue is common in mild or moderate hepatitis and studies using the short form with 36 items (SF-36) have demonstrated effects on general health, vitality, emotional well-being and ability to undertake social roles.

Treatment for HCV infection has undergone substantial changes in the last decade with the establishment of pegylated interferon combination therapy as standard treatment in many countries.

Sustained clearance of virus is achieved in up to 90% of recipients, although treatment is required for up to 48 weeks and is associated with reduced quality of life during that time.

Alcohol is an important determinant of progression of HCV disease, with increased consumption (over 50 g/day) being associated with a 60% increase in the relative risk of cirrhosis. About 40% of IDUs have high alcohol intake. Many studies have shown, in the general population, that brief counselling interventions are effective in reducing alcohol consumption.

Methods

A decision analytic model was developed to investigate the impact of case-finding and treatment on progression of HCV disease in a hypothetical cohort of 1000 people. This was compared with a cohort in whom no systematic case-finding is implemented but spontaneous presentation for testing is allowed to occur. A group of epidemiological and clinical experts informed the structure of the model, which has three main components: (1) testing and diagnosis, (2) treatment (3) long-term consequences of infection. A fourth component, case-finding strategies, examines the potential impact of case-finding in three settings: prisons, general practice and drug services.

The testing and diagnosis component of the model is a simple decision tree. Treatment is incorporated as part of a Markov model which represents the progression of HCV disease as transitions between discrete health states (mild, moderate or severe hepatitis; cirrhosis; decompensated cirrhosis; transplant and death).

Parameter estimates were obtained from literature searches, carried out on a range of electronic databases, and through contact with experts in the field. No methodological restrictions were applied, but searches were constrained to papers published or available in English.

Progression to cirrhosis was estimated from a meta-analysis of epidemiological studies. Other transition probabilities were obtained from literature review. Prevalences of risk factors for progression were obtained from a range of sources, including primary data from the Trent Regional Database Study. Data on costs and utilities of relevant health states were obtained from a recent trial of treatment for mild HCV disease. The effectiveness of combination therapy was estimated from a recent systematic review and meta-analysis. Effectiveness of brief interventions for alcohol reduction was obtained from a recent meta-analysis. Mortality from liver disease and other causes was estimated from routine UK mortality data.

Each cohort is assumed to be 37 years old at inception. The model runs for the lifetime of the cohort. Costs (base year 2004) and benefits [quality-adjusted life-years (QALYs)] were discounted at 6% and 1.5%, respectively.

Inherent uncertainty in the model was explored using extensive one-way sensitivity analyses, threshold analyses and probabilistic sensitivity analysis. A range of scenarios were explored using stochastic analyses. Value of information analysis was carried out to determine the value of further research.

Results

Case-finding for HCV is likely to prevent, for 1000 people approached, three cases of decompensated cirrhosis, three deaths due to HCV and one case of hepatocellular cancer (at 30 years). Twenty-five additional people are likely to undergo combination therapy as a result of initial case-finding. One liver transplant is likely to be prevented for 10,000 people included in case-finding.

Case-finding is likely to cost, in the general case, around £760,000 more than a policy of not case-finding. The total cost of either strategy is high and driven predominantly by the cost of treatment with combination therapy (the costs of long-term consequences are heavily discounted owing to the duration of the model). Systematically offering testing to 1000 people would cost around £70,000.

In terms of life-years gained, case-finding is likely to result in an additional life-year gained for an investment of £20,084. Taking impacts on quality of life into account gives an estimate for the cost–utility of case-finding as £16,514 per QALY.

The probabilistic sensitivity analysis shows that, if NHS policy makers view £30,000 per QALY as an acceptable return on investment, there is a 74% probability that case-finding for HCV would be considered cost-effective. At £20,000 per QALY, the probability that case-finding would be considered cost-effective is 64%.

The cost-effectiveness of case-finding in different settings is similar, although the absolute costs and benefits vary considerably. In all analyses, the probability of case-finding being considered cost-effective at a level of £30,000 per QALY was high. Case-finding in drug services is likely to be the most expensive, owing to the high prevalence of cases in the tested population. Correspondingly, benefits are highest for this strategy and cost-effectiveness is similar, in average terms, to the general case. Case-finding in general practice by offering testing to the whole population aged 30–54 years is, paradoxically, estimated to be the least expensive option. This is because, based on the only UK study of this approach, only a small number of people accept the offer of testing and HCV prevalence in this group is much higher than would be expected from the general population. This approach carries the theoretical advantage that it may reach people whose injecting drug career was many years previously and is not known to others. Two approaches to case-finding in prison were considered, based on the results of studies in Dartmoor and the Isle of Wight prisons. These differed substantially in the prevalence of cases identified in the tested populations. The analysis based on data from Dartmoor prison had the least favourable average cost-effectiveness of the strategies considered (£20,000 per QALY).

Subgroup analyses based on duration of infection show that case-finding is likely to be most cost-effective in people whose infection is more long-standing and who are consequently at greater risk of progression. In people who were infected more than 20 years previously, case-finding yields benefits at around £15,000 per QALY. The results are insensitive to many of the input parameters when these are varied across credible limits. In particular, the cost of the testing process does not impact significantly on the estimate of cost-effectiveness, mainly because a high proportion of the comparator cohort are expected to present for treatment during the course of the model and will undergo the same testing protocol. Treatment effectiveness was modelled using estimates from randomised controlled trials and lower rates of viral response may be seen in practice. However, estimates of cost-effectiveness remained below £30,000 for all levels of treatment effectiveness above 58% of those shown in the relevant trials.

The value of information analysis, based on assumptions that 10,000 people might be eligible for case-finding and that programmes would run for 15 years, suggests that the maximum value of further research into case-finding is in excess of £19 million. Partial expected value of perfect information (EVPI) analysis shows that the utility estimates used in the model eclipse all other factors in terms of importance to parameter uncertainty. This is not surprising, since the point estimates for differences in utility between states and across the arms of the model are small.

Implications for practice

Case-finding for HCV is already supported by national and international guidelines. The current assessment lends weight to these policies by demonstrating that case-finding is likely to be considered cost-effective when set alongside other potential uses of healthcare resources.

However, the estimated cost-effectiveness is not so favourable that all approaches could unequivocally be considered to represent good value for money. In particular, we have shown that strategies for case-finding that predominantly identify people early in the course of their disease may be less valuable than those which seek to identify those with more long-standing disease.

Although our findings suggest that case-finding is cost-effective, we have been unable, owing to the striking paucity of relevant data, to characterise with as much precision as we would like the configuration of real world approaches to case-finding.

Conclusions

Case-finding for hepatitis C is likely to be considered cost-effective by NHS commissioners. Although there remains considerable uncertainty, it appears unlikely that cost-effectiveness would exceed the levels considered acceptable.

Further improvements in the effectiveness of treatments to slow or halt disease progression are likely to improve the cost-effectiveness of case-finding.

Case-finding is likely to be most cost-effective if targeted at people whose HCV disease is probably more advanced.

Further empirical work is required to specify, in practice, different approaches to case-finding in appropriate settings and to evaluate their effectiveness and cost-effectiveness directly.

Further research

The following areas should be priorities for further research (in priority order):

1. Pilot studies of case-finding strategies are needed, in particular to develop methods of finding people who were infected decades ago and to evaluate uptake of testing, adherence and effectiveness of treatment.
2. Research into the benefits of case-finding followed by either treatment with combination therapy or approaches to behavioural modification which may result in benefits to infected and non-infected people who are currently injecting drugs.
3. Epidemiological research is needed to (a) monitor the scale and progress of the HCV epidemic and (b) estimate the number and type of IDUs across the UK in a wide range of settings in which case-finding might be considered.
4. Investigation of the effectiveness of harm reduction through advice to reduce alcohol intake in people with HCV is needed.
5. Research into the utility associated with disease states, treatment with combination therapy or counselling to achieve behavioural modification, and sustained viral response in current and former injecting drug users.
6. Studies on the effectiveness and cost-effectiveness of conventional and complementary treatment options such as low-dose pegylated interferon or dietary interventions, in terms of improving sustained viral response (SVR) rates and slowing disease progression.
7. Studies on the effect on SVR rates in former IDUs of using hepatitis nurse specialists (under the supervision of experienced consultants) in drug and alcohol units and prisons to improve treatment adherence.
8. Improved estimates of life expectancy in former IDUs.
9. Research into the knowledge and attitudes of clinicians and current and former IDUs towards HCV testing and treatment.
10. Studies on factors which may influence disease progression such as diabetes and obesity.

Chapter 1
Background

Epidemiology of hepatitis C

Hepatitis C virus (HCV) is a blood-borne virus causing slowly progressive chronic liver disease. The virus has six genotypes and many more subtypes. The most common genotypes in England and Wales are 1a (32%), 1b (15%) and 3a (37%).[1]

The virus is transmitted primarily as a result of contact with blood and blood products. The main route, since the introduction of effective screening of blood products, is the sharing of non-sterilised needles and syringes by injecting drug users (IDUs). There is also a small risk associated with body piercing, electrolysis, acupuncture and needle-stick injuries. Sexual infection and vertical transmission from mother to child can also occur, but are rare.

Acute infection

On exposure to the virus, virtually all patients develop liver cell injury, with evidence of elevated liver enzymes. Once infected, most people will develop chronic infection with persistent viraemia. Approximately one-fifth of patients will experience an acute hepatitis with associated malaise, weakness and anorexia.[2] There is some evidence to suggest that those who experience a symptomatic acute hepatitis are more likely to clear the virus quickly and may not progress to chronic disease.[3]

Chronic infection

Liver biopsy and serial measurement of liver enzyme levels are used to assess disease severity. Mild disease is characterised by a low level of necroinflammation in the liver with minimal or no fibrosis. Inflammation and cell death lead to the development of fibrosis in the liver. This becomes more severe with advancing disease and may culminate in cirrhosis. Cirrhosis is associated with complications such as portal hypertension, leading to oesophageal varices, and ascites or hepatic encephalopathy. HCV is also associated with the development of hepatocellular carcinoma (HCC). Fibrosis progression is typically slow, variable and often non-linear. Many patients remain asymptomatic until liver disease is advanced.

Hepatocellular carcinoma

Chronic hepatitis C infection is associated with increased risk of HCC. HCC appears to develop predominantly in patients with cirrhosis and, in most cases, occurs after 30–40 years of chronic infection. Estimates of the incidence of HCC in patients with hepatitis C vary owing to the paucity of long-term cohort studies; the best estimate is 1–3% over 30 years.[4] Estimates of annual incidence rates from cohorts of patients with cirrhosis are higher (1–5%).[4] This may be an artefact of more intense observation amongst this patient group. The prognosis for patients with HCC is poor. The median survival time was 17 months (range 1–60 months) in a recent prospective cohort study of 102 cirrhotic patients with HCC.[5]

Risk factors for disease progression

Factors positively associated with the rate of fibrosis progression include male sex, heavy alcohol consumption, elevated liver enzyme levels and the degree of fibrosis and inflammation at biopsy.[6] Other studies have also found older age at infection and duration of infection to be important.[7–9] Risk factors for progression to HCC include alcohol consumption, male sex and race.[10] The relationship between genotype and disease progression is unclear. Several studies suggest no correlation.[7,11] However, a large cohort study (n = 2307 patients with histologically proven hepatitis C) found that genotype 1b was associated significantly with both cirrhosis and the development of HCC.[12] It is important to note that very long-term data on the nature of progression of HCV are not yet available.

Co-infection with hepatitis B and HIV

Several studies suggest that both hepatitis B and HIV co-infection may modify the natural history of hepatitis C infection, leading to a faster rate of progression to end-stage liver disease.[13–14]

Prevalence of hepatitis C infection in the UK

It is estimated that 0.4% of the general population in England and Wales have chronic HCV infection.[15] Between 1992 and 2003, 41,512 diagnoses of hepatitis C were reported to the Communicable Disease Surveillance Centre in

TABLE 1 *Hepatitis C prevalence in injecting drug users in 2003 (by gender and age)*

	Hepatitis C prevalence (%)	
Age (years)/gender	**London**	**Outside London**
<25	28	17
25–34	50	33
≥35	57	52
Male	54	36
Female	51	33
All	53	35

England and Wales. The majority of cases were in the age groups 25–34 years (35%) and 35–44 years (28%); two-thirds were male.[16] Over 90% of those for which the information is provided gave injecting drug use as the principal risk factor.[16]

Epidemiology of hepatitis C in injecting drug users

There is no evidence to suggest that past or current injecting drug behaviour or the route of transmission has any causal effect on disease progression. Risk factors for acquiring hepatitis C amongst IDUs include age, duration of injecting career, crack cocaine use, forming of injecting or sexual partnerships and consequent sharing of needles and drug preparation equipment.[17]

Prevalence of injecting drug users in the UK

The extent of injecting drug use and the prevalence of people with a history of injecting drug use in the UK are uncertain.

There are several estimates of the prevalence of current IDUs. A national estimate of prevalence for Scotland suggests that 0.8% (25,000) of the Scottish population aged between 15 and 54 years were drug misusers injecting opiates or benzodiazepines in 2000.[18,19] A report published by the Home Office in 2004 estimates that 0.2% of the total population of England were IDUs in 2001,[20] although this result is likely to be an underestimate owing to reliance on registration data. A recent study of the level of injecting drug misuse in three cities in England suggests that between 1.2% (London) and 2.0% (Brighton) of adults aged between 15 and 44 years were IDUs in 2000–2001, although these cities are believed to be areas of particularly high prevalence.[21]

The prevalence of people who have ever injected drugs has also been estimated. The community-based National Survey of Sexual Attitudes and Lifestyles (NATSAL), published in 1990, estimated that 0.8% of adults in England and Wales had ever injected drugs.[22] Using three different approaches, Bird and colleagues estimate that between 240,000 and 835,000 people in England and Wales have ever injected drugs, with a preferred estimate of around 360,000.[23]

The prevalence of former IDUs, which is central to this assessment, is more difficult to estimate. Back-calculation methods provide some estimates, ranging from 0.22% to 0.8%, depending on the rate of cessation of injecting and the inclusion of time and age-specific mortality data.[24] An important area of uncertainty remains the proportion of people who are recreational as opposed to dependent users of drugs by injection. De Angelis and colleagues[24] were unable to obtain data on this group and NATSAL data are subject to social desirability and recall biases. Current estimates of the size of the population of interest may be underestimates.

Incidence and prevalence of hepatitis C amongst injecting drug users in the UK

A prospective cohort study conducted in new IDUs in London and Brighton in 2001 suggests a high prevalence and rising incidence of hepatitis C infection. The baseline prevalence of antibody to hepatitis C was 44%. After 12 months of follow-up, the cumulative incidence of hepatitis C antibody was 41.8 cases per 100 person-years.[25] In 2003, 41% of those taking part in the Unlinked Anonymous Prevalence Monitoring Programme (UAPMP), a survey of current and former IDUs in contact with drug agencies, had antibodies to the HCV. A breakdown by age and gender is shown in *Table 1*. There were marked regional differences in

TABLE 2 *Hepatitis C prevalence in injecting drug users in 2003 (by region)*

Region	Hepatitis C prevalence (%)
East of England	30
London	53
South East	31
South West	30
West Midlands	21
North West	56
Yorkshire and Humberside and East Midlands	41
North East	18
Wales	16
Northern Ireland	17

TABLE 3 *Relationship between the proportion of patients with a positive anti-HCV test and the source of referral*

Source of referral	Proportion of patients with positive anti-HCV test
General practice	56/2832 (2.0%)
Prisons	38/202 (18.8%)
Drug and alcohol units	61/323 (18.9%)
Secondary care	101/7646 (1.3%)

these data, with 18% of responders in the North East having antibodies compared with 53% in London and 56% in the North West of England (*Table 2*).

A retrospective cross-sectional study performed in Nottingham analysed the outcome of all serum samples sent to the public health laboratory during a 2-year period (Irving W, University of Nottingham: personal communication, 2005). Overall, samples from 11,073 individuals were received. A total of 256 (2.3%) of these were positive for HCV antibodies. The proportion of positive tests varied considerably depending on the source of referral (*Table 3*), although it should be noted that no data are available on reason for exposure to HCV by source.

Case-finding for hepatitis C

Case-finding refers to efforts to identify hepatitis C in people who are unaware of their status by offering testing, using a sequence of tests enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) followed by staging of disease (where appropriate) and treatment (where eligible). Counselling is needed prior to the offer of testing so that recipients are aware of the implications of the test and can give informed consent.

Following the convention of the UK National Screening Committee, case-finding is considered to be distinct from population screening because the target population already has a health problem, injecting drug use, of which HCV infection is a recognised complication. It is recognised that this distinction is contradicted by the widespread use of the term 'screening' to refer to systematic efforts to identify complications in people with diabetes. However, the term 'screening' in diabetes is very well established and is considered an exceptional case.

A wide range of approaches to case-finding are possible. In this report, three settings are considered: prisons, drug and alcohol services and general practice. In the first two, a high proportion of people with a history of injecting drug use may be encountered. General practice is included as it presents an opportunity for case-finding, given that a high proportion of the population come into contact with primary care services each year. Case-finding and opportunistic health promotion are well established in general practice, for example, for hypertension or to promote smoking cessation.

The Chief Medical Officer recently identified hepatitis C as needing 'intensified action' to improve prevention, diagnosis and treatment. This resulted in the publication of the *Hepatitis C Action*

Plan for England in 2004,[26] the aims of which are to improve surveillance and research, increase awareness of hepatitis C and thereby reduce undiagnosed infections, to ensure that high-quality services for assessment and treatment are coordinated and accessible to patients and to intensify prevention efforts to reduce the spread of the disease in high-risk populations. More recently, the All Party Parliamentary Group on Hepatology has urged the government to revise the Action Plan, calling for greater investment to deal with the virus and a proactive testing programme targeted on risk groups.

The Royal College of Physicians of Edinburgh's recent Consensus Conference on Hepatitis C concluded that 'a high priority for case-finding should be given to former IDUs, especially those over 40…'.[27] The EASL Consensus Statement on Hepatitis C advises that screening should be limited to risk groups such as current or previous users of intravenous drugs.[28]

Current status of case-finding in the UK

A survey of prisons, health authorities, drug services and genitourinary medicine (GUM) clinics conducted in 2002 found that case-finding for hepatitis C infection was most prevalent in GUM clinics and prisons (92% and 78%, respectively, reporting that screening was conducted by their organisation), with fewer health authorities and drug services (28 and 26%) providing this service. A wide range of eligibility criteria for screening were used with the majority of organisations screening only those considered to be at increased risk of infection.[29]

There are few data describing the uptake of HCV testing where it is offered. Studies based mainly in prison populations suggest an uptake of 10–50%, with higher report rates in locations where testing was particularly promoted.[30] In 2003, only 53% of infected responders taking part in the Unlinked Anonymous Prevalence Monitoring Programme (UAPMP) were aware of their status.[31]

General practice

No published reports of case-finding were found within general practice in the UK. There is one unpublished example of opportunistic case-finding performed in an area of high deprivation and presumed high HCV prevalence in Scotland. In this example, all patients within the age group 30–54 years who attended the surgery for a routine appointment were offered the opportunity to make an appointment for pre-test counselling for hepatitis C. About 50% of the target population attended the surgery at least once during the study period (6 months), 10% volunteered for testing and 12.5% of these were antibody positive (Anderson E, Department of Public Health, Lanarkshire NHS Board: personal communication, 2005).

Prisons

There are two published examples of case-finding programmes conducted within prisons in the UK. In Her Majesty's Prison Dartmoor, all new prisoners are offered an HCV test. Education on blood-borne viruses is provided during the induction process, with individual pre-test counselling for those prisoners who accept the offer of testing. The initial ELISA test is performed in the prison with referral to a specialist unit for those with a positive HCV antibody result. An observational study published in 2004 found that of 3034 new prisoners entering the prison, 12% were tested for HCV and 16% of these were seropositive.[32] The second study was an evaluation of an outreach clinic established in the Isle of Wight prison cluster to improve the quality of care offered to prisoners with HCV. A total of 1618 prisoners entered the prisons in the 1-year study period, 8.5% volunteered for hepatitis C testing following a health awareness lecture and 42% of these were antibody positive.[33]

Drug and alcohol services

Some drug and alcohol services routinely offer tests for hepatitis C to current and former IDUs [see the section 'Current status of case-finding in the UK' (previous column)]. There are, however, few published examples of opportunistic case-finding programmes or reports of the level of uptake and referral in this population.

The National Treatment Agency for Substance Abuse is currently revising its Models of Care for the treatment of adult drug misusers, which is a framework for developing local systems for effective drug misuse treatment in England.[34] It emphasises the importance of a local protocol for referring clients for health screening and testing for blood-borne diseases and of the need for liaison between specialist services. It recommends that all services should provide information and advice to individuals about access to testing for hepatitis C and should be able to talk to drug users with whom they come into contact about raising awareness of risks associated with blood-borne diseases. As part

of the new Models of Care, services will be required to collect data on levels of uptake and referral for testing for blood-borne viruses.

Cost-effectiveness of case-finding in the UK

To our knowledge, there have been no further publications on the cost-effectiveness of case-finding for hepatitis C in IDUs in the UK since the publication of our previous work in this area.[29] Previous publications have shown that treatment of IDUs with a combination of interferon (IFN) and ribavirin is more cost-effective than treatment with interferon IFN monotherapy,[35] but none has examined the cost-effectiveness of combination therapy with pegylated interferon (PegIFN) and ribavirin in this group.

Methods of case-finding and diagnosis

Enzyme-linked immunosorbent assay (ELISA)

HCV antibody testing by ELISA is the initial test used to identify patients with hepatitis C infection. Antibodies specific to HCV infection are detected by ELISA techniques using recombinant HCV antigens. The presence of HCV antibodies suggests exposure to HCV but gives no indication as to whether infection is ongoing. Newer generation ELISA tests have a high level of sensitivity and specificity, although false-positive results are possible. A recent systematic review of the performance of serological tests for HCV reported the specificity and sensitivity of third-generation ELISA tests in chronic liver disease as 97.2% [95% confidence interval (CI) 92 to 99%] and 100% respectively.[36]

Reverse transcription polymerase chain reaction (PCR)

PCR detects circulating HCV RNA in the blood and is therefore an indication of current infection. HCV RNA can be found in the blood 1–3 weeks after infection and its continuing presence beyond 6 months indicates chronic infection. Commercially available tests for HCV RNA have a high level of sensitivity and specificity. One manufacturer of PCR tests (Roche Diagnostics) reports values of 99.8 and 99.3% for sensitivity and specificity, respectively, when testing against a known infected sample of serum. Current British Society of Gastroenterology guidelines recommend that HCV RNA testing be repeated using a recombinant immunoblot assay in HCV antibody-positive patients initially achieving a negative PCR result.[37]

Liver biopsy

Liver biopsy is used to assess the status of the liver for inflammation, potential progression of fibrosis and the presence or absence of cirrhosis. Results are graded using the Histological Activity Index (HAI) and scored most commonly with the Ishak[38] and METAVIR scoring systems.[39] Liver biopsy is associated with some complications, the most common being transient pain. More serious but less common complications include bleeding, biliary leak, intestinal perforation, vasovagal hypotension and infection. In a case series of 2084 percutaneous liver biopsies performed in France, 0.58% of patients experienced adverse events, defined as vasovagal, haemoperitoneum, biliary peritonitis, pneumothorax and punctures.[40] Information gained from biopsy can be important in assessing the need for antiviral treatment. However, recent approaches to treatment[41] are less dependent on disease severity, thus reducing the need for biopsy at the time of diagnosis.

Treatment

Drug therapy

The technology assessment report commissioned by the HTA programme on behalf of the National Institute for Health and Clinical Excellence (NICE) and published in 2004 recommends PegIFNα and ribavirin as the standard treatment for chronic HCV infection.[42] Clinical trials in patients with moderate to severe disease have demonstrated overall sustained virological responses of 54% and 56% with 48 weeks of combination therapy.[43,44] Response rates are highest in patients with genotype 2 or 3, who have an 80% or greater chance of achieving a sustained virological response to treatment. The recently published randomised controlled trial (RCT) in patients with histologically mild disease, which compared treatment with non-PegIFNα 2b and ribavirin for 48 weeks with no treatment, demonstrated a sustained viral response in 33% of patients in the treated group.[45] As with moderate to severe disease, patients infected with genotype 1 had a lower response rate than those infected with a non-1 genotype (18 vs 49%). The most common side-effects of treatment are fatigue, headache, myalgia, rigors, fever, nausea, insomnia and depression. Approximately 60% of patients in one trial reported symptoms of fatigue, headache and myalgia. Rigors, fever, nausea and insomnia

were less common, with just less than half the patients experiencing these.[43] Neutropenia and anaemia are more serious but less common side-effects that can necessitate dose reduction or, rarely, discontinuation of treatment.[42] In one trial, 9% of patients experienced anaemia and 18% were found to have neutropenia.[43]

Eligibility and suitability for treatment depend on the degree of liver damage, the level of hepatic and extra-hepatic symptoms, the presence of serious co-morbidity (medical or psychiatric), patient preferences and ongoing substance abuse. Absolute contraindications to treatment are defined as pregnancy, allergy to interferon or ribavirin, decompensated cirrhosis, continued intravenous drug use and heavy alcohol use. Relative contraindications to treatment include anaemia, leucopenia, thrombocytopenia, autoimmune disease, coronary artery disease, severe psychiatric disease and current or historical psychoses. Observational studies in three populations in the USA found that 30–40% of evaluated patients received treatment.[46]

A meta-analysis of three RCTs and 15 non-RCTs, including 4614 patients, suggests a small preventative effect of IFNα on hepatocellular carcinoma development, most evident in patients with a sustained response to IFNα.[47] There is currently no recommended antiviral therapy for decompensated cirrhosis.

There is currently no compelling evidence for any complementary or alternative therapy in the treatment of chronic hepatitis C.[48]

Liver transplant

Once hepatic decompensation or HCC has developed, liver transplantation is the only potentially curative treatment available. Complications of HCV-related cirrhosis are the leading indication for liver transplantation in Western Europe. The proportion of liver transplants carried out in former IDUs is uncertain, but probably varies between transplant units and is changing. For example, a large proportion of people who underwent liver transplant in the early 1990s for HCV disease came from a cohort of HCV-positive Asian immigrants. Expert opinion suggests that around 75% of cases of transplantation are in former IDUs (Mutimer D, University of Birmingham: personal communication, 2005).

Recurrence of hepatitis C infection occurs in all patients who are HCV RNA positive and can follow an aggressive course. Tumour recurrence can also occur.[49] A study of 300 patients receiving a liver transplant for chronic hepatitis C found histological recurrence in 40% within a 2-year follow-up period; 14% developed cirrhosis.[49] Approximately 30% of patients will die or require re-transplantation within 5 years of the transplant.[50,51]

Alcohol harm reduction

Heavy alcohol intake has been identified as an independent risk factor for the progression to cirrhosis in several studies.[52] There is some evidence to suggest that knowledge of hepatitis C status influences attitude to alcohol consumption, with fewer hepatitis C-positive people drinking alcohol in one survey of opiate users in treatment.[53] Although now dated, our previous review found no compelling evidence to support the idea that knowledge of HCV status had any effect on either drug-related or sex-related behaviour, and this may also be the case for alcohol consumption.[29] Patients who are ineligible for drug therapy may receive counselling to reduce alcohol consumption.

Impact of hepatitis C infection on quality of life

In the general population

Many studies using health status assessment instruments such as the Short Form with 36 items (SF-36) and preference-based approaches have demonstrated impairments in quality of life (QoL) associated with chronic hepatitis C infection.[54–59] Deterioration in QoL is linked to disease severity, with non-cirrhotic and compensated cirrhotic patients having similar scores, decompensated cirrhosis being associated with the worst scores and transplanted patients showing a significantly better QoL than cirrhotic and non-cirrhotic patients with liver disease.[57,58,60] The most important effect of chronic hepatitis C is on the physical domains of QoL.[57,58]

SF-36 data from Chong and colleagues,[58] in 193 Canadian people with varying severity of HCV disease, show that even mild/moderate disease is associated with QoL levels that are significantly lower than norms for the general population. Mild or moderate disease was associated with around 5–10% decrements in scores in the domains of physical functioning, role physical, vitality, general health, social functioning and role emotional. Fatigue is often reported in mild or moderate disease. This is not measured directly in the SF-36, although the vitality domain may be expected to reflect this symptom.

Early modelling studies of the cost-effectiveness of antiviral treatment relied on expert opinion of the impact of disease on QoL. Chong and colleagues have demonstrated that such estimates tend to underestimate the impact of mild and moderate disease and overestimate the impact on QoL of decompensated cirrhosis and hepatocellular carcinoma.[58]

Successful antiviral treatment has been associated with improvements in health-related QoL.[45,55,61]

In injecting drug users

No specific data were found on the QoL of people with a history of injecting drug use. In one study, the health-related QoL scores of current IDUs were shown to be lower than the reported normative data for the Norwegian population.[62,63] However, there were no differences in QoL scores between injecting drug users with chronic hepatitis C infection and those without. In addition, hepatitis C-positive patients who were aware of their status had lower scores than those who were unaware of their status.[62]

Chapter 2
Methods

Overview

Research question

The question addressed by this HTA is:

- What is the clinical effectiveness and cost-effectiveness of testing for hepatitis C virus (HCV) in former injecting drug users? (Appendix 2)

In this context, testing is defined as including efforts to identify people in the population with HCV infection and to offer them testing, that is, systematic case-finding.

General approach

The research question was addressed by the development of a new decision analytic model to explore the impacts of systematic case-finding for HCV in a general case and in three potential health service settings. The model, described in full in subsequent sections, synthesises information on all stages of case-finding, compared with diagnosis being carried out in response to patient request: spontaneous (where no previous offer of testing has been given) or re-presentation (where a previous offer was made but testing was not carried out).

The modelling study updates the previous assessment[29] with more recent information on different aspects of case-finding, treatment and long-term consequences of infection. It also extends previous methods by incorporating probabilistic sensitivity analysis (PSA) and estimating expected value of perfect information (EVPI). PSA takes account of joint uncertainty in model parameters. EVPI indicates the maximum value of further research (i.e. the value of eliminating decision uncertainty) and identifies those aspects of the model for which further information may be most valuable. Furthermore, several specific approaches to case-finding in different settings are explored:

- general practice
- drug services
- prisons.

These are described in more detail in the section 'Case-finding strategies in different settings' (p. 25).

In all cases, systematic case-finding is compared with non-case-finding, that is, people may spontaneously present for investigation, either in response to concerns about possible infection or because of the development of symptoms.

The population of interest is **former** IDUs. A programme of case-finding and treatment in people who are **currently** IDUs is not considered. This reflects current guidelines that treatment of chronic HCV infection should be restricted to people who are not currently injecting.[37]

Effectiveness of case-finding for HCV is estimated by calculating the number of additional people who achieve a sustained response from treatment as a result of systematic case-finding and, consequently, the number of cases of serious long-term sequelae from chronic HCV infection which may be prevented by case-finding. Costs (£) are estimated from the perspective of the NHS, using 2004 as the base year. Costs are discounted at 6% and health benefits at 1.5% per annum. Other discount rates have been used in the sensitivity analyses.

Results are reported in three complementary ways:

1. Costs and consequences for case-finding and non-case-finding are presented separately for descriptive purposes.
2. The costs of case-finding, spontaneous presentation, treatment of HCV infection and management of long-term sequelae are synthesised with estimates of treatment effectiveness and long-term consequences of infection to estimate cost-effectiveness [cost per life-year gained (LYG)].
3. Outcomes are also described in terms of quality-adjusted life-years (QALYs) and combined with cost estimates to calculate the incremental cost–utility (cost per QALY) of systematic case-finding.

Model development

The model was developed in Microsoft Excel®. A group of epidemiological and clinical experts provided advice on development. The model follows two hypothetical cohorts of people: those in whom systematic case-finding is applied and the

comparison group in whom only spontaneous presentation occurs. The general case analysis evaluates case-finding from the point of offering an ELISA test. Further analyses explore the potential effectiveness and cost-effectiveness of identifying people with HCV in three settings (prisons, drug and alcohol services, and general practice), based on available data.

Structurally, the model has four main components.

1. **Testing and diagnosis**. From the point of offering ELISA testing through to the offer of treatment using combination therapy. The analysis combines the performance of ELISA and PCR testing with information on eligibility for biopsy, acceptance and adverse events using a decision tree.
2. **Treatment**. In eligible cases, treatment is with PegIFN and ribavirin combination therapy. Reduction in alcohol consumption is advised for all tested cases.
3. **Long-term consequences**. The long-term consequences of HCV infection are modelled in both arms of the model for people who are not identified for testing through case-finding and who do not present spontaneously (using a Markov approach).
4. **Case-finding strategies**. A range of possible approaches to case-finding in three settings (general practice, prisons and drug services) are explored using simple proportions to estimate uptake of initial ELISA testing.

Treatment and diagnosis and **long-term consequences** are time dependent. They are therefore modelled using a state-transition (Markov) approach in a hypothetical population. The disease process is represented using a series of possible transitions between discrete health states, occurring at fixed time intervals (cycle length). In this case, the cycle length is 3 months. Total costs and health outcomes are estimated over the total lifetime for the population attaching cost and QoL (utility) weights to the amount of time spent in each state. This model follows two hypothetical cohorts of people: those in whom systematic case-finding is applied (case-finding arm), after which untested patients may re-present for testing at a later date; and the comparison group in whom spontaneous presentation for testing occurs throughout the model (non-case-finding arm). The cost-effectiveness of systematic case-finding is then calculated as the difference in total cost between the two cohorts relative to the difference in QALYs gained.

All analyses start with the identification of individuals for ELISA testing. In the general case, general data are considered for the population tested and the costs associated with testing during a 2-minute consultation with a generic healthcare provider. This examines, in general terms, the cost-effectiveness of testing and subsequent treatment. Time is not explicitly modelled in the **Testing and diagnosis** component of the model. It was assumed that the testing and diagnosis steps in management would take place within a 3-month period (the 'Markov cycle length'). The **Case-finding strategies** component of the model explores the potential performance of efforts to identify people for testing within defined settings. Again, time is not considered in this component.

Case-finding strategies clearly apply only to the cohort where testing is being actively promoted. The other elements of the model are used in both cohorts. For example, people who spontaneously present for testing may receive treatment and people who refuse testing as part of systematic case-finding are subject to assumptions regarding long-term progression.

At the start of the analytic time horizon, both cohorts are assumed to have an average age of 37 years, based on data from the Trent HCV Study Cohort Database (Irving W, University of Nottingham: personal communication, 2004).

Within each strategy, the cohort is followed until all members of the cohort have died.

Obtaining model inputs

Initially five literature searches related to chronic hepatitis C in IDUs were conducted in the following areas using electronic databases (for full details, see Appendix 1):

1. natural history of HCV
2. acceptability of testing procedures and adherence to antiviral treatment
3. effectiveness of antiviral treatment
4. costs of long-term complications of HCV and the treatment of advanced liver disease
5. QoL.

The search strategies were developed, tested and refined by an information scientist (AP). Searches 1 and 2 were limited from 1996 as similar searches had been performed for the report completed in 2001.[29] Search 3 was limited from 2003 as a systematic review of combination therapy was identified which carried out searches up to March 2003.[41] Searches were not limited by

methodological features but were limited to the English language. Two reviewers screened titles and abstracts of identified studies for relevance to the model. During the implementation of the model, particular efforts were made to obtain relevant literature in areas where there was a paucity of published data, such as acceptability of testing procedures, mortality from liver cancer and the prevalence of former IDUs in the UK. Additional data were retrieved from scrutiny of reference lists in retrieved papers and contact with experts in the field. No handsearching was carried out.

Values included in the model were chosen on the basis of methodological quality of the study, publication date (favouring more recent studies), relevance to the UK, the sample size of the study and the appropriateness of the study population.

Unpublished data from the Trent HCV Study Cohort database was obtained from Professor William Irving and used to inform the model. Where necessary, data were analysed to bring them into a form appropriate to the model using Stata® software.

Model structure and data inputs

This section describes the various pathways that are evaluated in the model and details the sources of data and values synthesised to estimate effectiveness and cost-effectiveness.

All strategies, including the general case, lead to a common testing and diagnosis pathway that begins with the ELISA test and proceeds, where appropriate, to treatment/advice. Initially, the general case is considered, and subsequently, the different settings are evaluated in turn. A summary of the main differences in data inputs between the various strategies are highlighted later in *Table 18*.

Population characteristics

Unpublished data from the Trent HCV Study Cohort Database were used to inform several of the parameters surrounding the characteristics of the cohorts in the model. These data were chosen because they represent a large UK cohort of patients with hepatitis C with a documented risk factor of injecting drug use.

Prevalence of HCV

Several studies have reported the prevalence of HCV amongst IDUs in different populations, such as prison inmates, liver clinics and drug and alcohol services, in England and Wales.[64–66] Bird and colleagues[30] conducted a review of these studies and produced a pooled estimate of 49% (95% CI 38 to 61%). The pooled estimate is used in the model as this reflects the prevalence of HCV in a range of different settings. The prevalence of HCV viraemia is calculated by adjusting for spontaneous clearance of HCV in the acute phase. A figure was obtained from the Trent Database as this provides the best available UK estimate of the proportion of people who undergo spontaneous clearance (18.6%).[67] The prevalence of chronically infected individuals in the model cohort is therefore approximately 40%.

Genotype

Data on the genotype distribution in the target population are taken from the Trent HCV Study Cohort Database: 51.6% genotype 2 or 3 and 48.4% genotype 1, 4 or 5.[67] These proportions were assumed to apply to people whose status is currently unknown.

Age and severity of liver disease

Information on age and severity at presentation was obtained from individuals within the Trent HCV Study Cohort Database with a risk factor of injecting drug use (Irving W, University of Nottingham: personal communication, 2004). The average age at presentation in the Trent cohort was 37 (±8.5) years, and this is used as the age at presentation in the general case analysis. The corresponding spectrum of severity (based on Ishak scores) at presentation is shown in *Table 4*. This also shows the features of subgroups according to duration of infection. This was calculated as age at biopsy minus age at infection and grouped by infection duration into: <10 years, 10–19 years, 20–29 years and ≥ 30 years. The average age of people in each of these groups was then calculated and formed the basis for subgroup analyses of the cost-effectiveness of case-finding.

As expected, severity varies by age at first biopsy, since this is associated with length of infection. Individuals tested at early ages show aggressive patterns of disease in a very small number of cases (1.3%) whereas individuals with a very long history of infection still show a mild disease in the majority of cases (54%). However, progression to severe stages of the disease occurs in up to 27% of the longest infected individuals. This still constitutes a significant burden of disease since up to 30% of individuals have reached severe stages of the disease by the age of 50 years.

TABLE 4 *Average duration of infection, age at infection and severity of liver disease at first biopsy*

	Duration of infection from first exposure to IDU (years)				
	0–9	**10–19**	**20–29**	**30+**	**Overall**
Average length of infection (years) (SD)	5.7 (2.3)	14.5 (3)	23.4 (2.8)	33.6 (3.1)	20.8 (5.9)
Average age at infection (years) (SD)	23.7 (7)	21.1 (5.3)	19.6 (4.7)	15.7 (5.2)	16.9 (8.4)
Average age at presentation (years)	29	35	43	50	37
Mild (SE) (%)	96.3 (2.1)	77.5 (3.5)	63.2 (4.3)	53.8 (9.9)	75 (2.2)
Moderate (SE) (%)	2.5 (1.8)	14.7 (3.0)	18.4 (3.5)	19.2 (7.9)	13.7 (1.8)
Severe (SE) (%)	0	4.9 (1.8)	7.2 (2.3)	15.3 (1.25)	5.4 (1.2)
Cirrhotic (SE) (%)	1.3 (1.3)	2.8 (1.4)	11.2 (2.8)	11.5 (6.4)	5.9 (1.2)
N	80	142	125	26	373

SD, standard deviation; SE, standard error.
Source: Irving WL, University of Nottingham: personal communication, 2004.

Severity appears skewed towards mild disease at presentation. This finding differs from previous reports on stage at presentation from tertiary centres, which suggest that severity may be more advanced at presentation. However, this may be due to several factors. First, people treated at tertiary centres may have more severe disease. Second, the previous restriction of treatment to people with moderate to severe disease may mean that younger patients, whose disease may be assumed to be less severe, may have declined biopsy and so data from biopsy series would be more biased towards more advanced disease. Third, younger people, with milder disease, are more likely still to be injecting and may not have had a biopsy because of this contraindication to treatment or, possibly, less concordance with biopsy.

It was assumed that the distribution of severity in cases identified through systematic case-finding or at spontaneous presentation is the same as that of patients in the Trent HCV Study Cohort Database. As noted, these data appear skewed towards the milder end of the spectrum of liver disease. This may be due, in part, to the inclusion of cases that were identified through existing case-finding programmes. We are not aware of any UK study which has collected information on how people came to be tested for HCV, making this problem currently intractable. Anecdotally, current UK HCV cohorts vary according to severity mix, emphasising further the uncertainty around this issue.

It is not possible to predict the magnitude of the bias arising from the application of these data to the modelled populations. However, it is likely that severity at spontaneous presentation will have been underestimated and severity in the population identified by case-finding will be overestimated. The impact of varying assumptions about severity distribution at diagnosis in each cohort is examined in the analysis of uncertainty.

Testing and diagnosis

Figure 1 shows the clinical pathway from ELISA testing to consideration of treatment. Individuals who decline testing and those who are lost to follow-up or misclassified as false negatives during testing and diagnosis proceed with the natural history of infection. At the end of this sequence, all individuals transfer to the **Long-term disease progression** component of the model. The sequence of testing in the model is based on an algorithm derived from national[37,68] and local guidelines (Cramp ME, Derriford Hospital, Plymouth: personal communication, 2004).

ELISA and PCR testing

ELISA and PCR are highly sensitive and specific tests for, respectively, antibodies to HCV (indicating past exposure) and HCV RNA (indicating chronic infection).

The technical performance of ELISA testing was estimated from a recent systematic review and meta-analysis of third-generation tests in HCV.[36] Specificity was 97.2% (95% CI 92 to 99%) and sensitivity was 100%. Values between 90 and 100% are explored in the sensitivity analyses.

Data on the diagnostic performance of PCR testing were obtained from a manufacturer of PCR test kits (Roche Diagnostics), as reported in the previous HTA.[29] Reported sensitivity and specificity of 100% were based on testing a

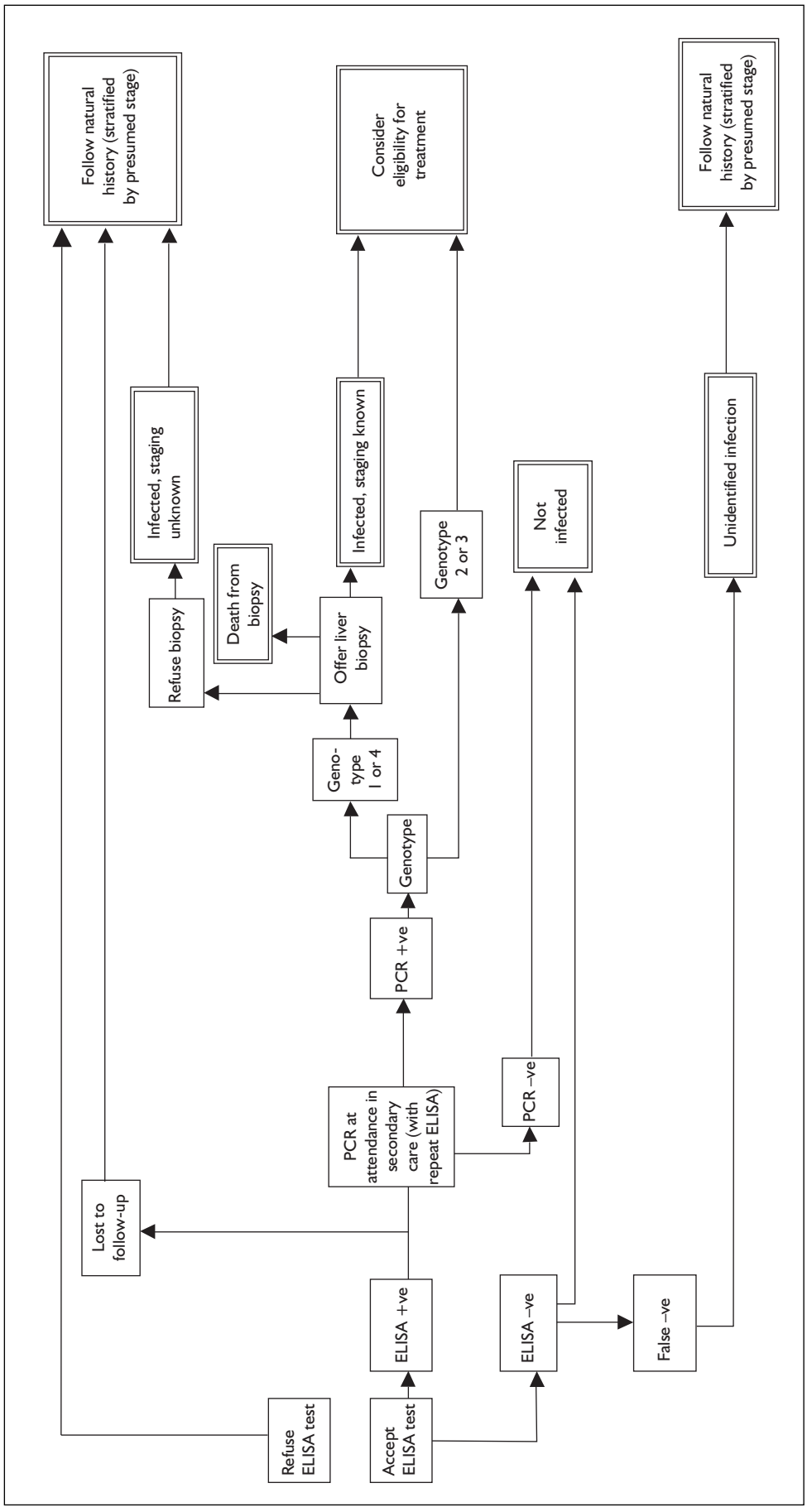


FIGURE 1 *Testing and diagnosis*

TABLE 5 *Acceptance of ELISA testing*

Study	Setting	Tests performed	Comments
Serfaty *et al*., 1997[70]	Drug and alcohol service	49% (99/202)	98/202 were former IDUs 104/202 were current IDUs
Anderson (personal communication, 2005)	GP practice in Scotland	10% (117/1165)	Population-based approach. 13/117 were former IDUs, 4/117 were current IDUs
Horne *et al*., 2004[32]	Dartmoor Prison	12% (364/3034)	Population-based approach Risk factor data were not collected
Skipper *et al*., 2003[33]	Isle of Wight prison cluster	8.5% (137/1618)	Population-based approach 96% of people tested had a history of IDU, although the proportion of IDUs in the target population is not known
Meachin (personal communication, 2005)	Drug and alcohol services, Devon	52% (99/192)	

standard plasma sample provided by the WHO. Slightly lower estimates were obtained when testing against a known sample of serum (sensitivity 99.8% and specificity 99.3%). Values between 90 and 100% are explored in the sensitivity analyses. Recombinant immunoblot assay (RIBA) testing is not used in diagnosis.

Patients with positive ELISA have a second sample taken for repeat ELISA and PCR testing at the first attendance at specialist outpatient services.

False-negative classification on PCR or ELISA leads to cases following the natural history of HCV progression.

False-positive results are believed to occur mainly as a result of sample cross-contamination, which is rare in this high-risk group.[69] The sequence tests give extremely high specificity: assuming independence of ELISA results, the false-positive rate after PCR is around 1 in 700,000 people tested. Patients who have a positive ELISA but negative PCR have cleared the virus spontaneously and are discharged from follow-up.

Acceptance of ELISA

In the general case, to reflect the steps prior to ELISA being carried out, it is assumed that only a proportion of people offered testing will undergo it. There are very few data on acceptance of ELISA testing in people with a history of injecting drug use. *Table 5* summarises available estimates on the acceptance of ELISA testing. Studies by Serfaty and colleagues[70] and Anderson (Anderson E, Department of Public Health, Lanarkshire NHS Board: personal communication, 2005) report acceptance in IDUs, broken down by current and former use. The population-based studies report a much lower acceptance rate, reflecting that fewer people within the cohort have a potential risk factor for HCV infection.

The study by Serfaty and colleagues[70] therefore provides the most suitable estimate (49%) for the general case as it is derived from a targeted approach in an IDU population. Other estimates were considered more suitable for the case-finding scenarios, and these are described in the section 'Case-finding strategies in different settings' (p. 25).

People who are offered ELISA and refuse, or who are ELISA positive but do not receive PCR, are assumed to have the same HCV prevalence as the rest of the IDU population.

Acceptance of PCR

It was assumed that PCR testing is carried out on a new blood sample, taken when the patient attends secondary care. Data on attendance at this stage in the clinical pathway are difficult to interpret (*Table 6*) as some papers report the proportion of people referred for specialist management (the definition of which may vary depending on the health system) whereas others report actual attendance. There is considerable variation in the reported proportion of referred patients. There is also some variation in practice, for example, in the unpublished study by Anderson, ELISA and PCR were performed on the same sample and only PCR-positive patients were referred for specialist management (Anderson E, Department of Public Health, Lanarkshire NHS Board: personal communication, 2005). Similarly, in Plymouth, the PCR test is performed prior to referral (Meachin C, Derriford Hospital, Plymouth: personal communication, 2005).

TABLE 6 *Referral to and attendance at specialist services*

Study	Setting	Referral to specialist management	Attendance at specialist services	Comments
Mohsen *et al*., 2001[67]	Non-specific	55%		Data from the Trent HCV Study Cohort Database cohort
Irving *et al*. (personal communication, 2005)	All GPs Prisons DAU	48.8% 66.1% 18.4% 42.6%	79.8% 78.1% 100% 47.4%	$n = 256$ 32 patients were aged <25
Jowett *et al*., 2001[71]	Liver clinic		79%	All had injecting drug use as main risk factor
Horne *et al*., 2004[32]	Dartmoor Prison	64% (29/45)		Risk factor data were not collected Undifferentiated testing offer to all inmates
Smyth *et al*., 2000[72]	Outpatient addiction clinic, Ireland	77% (20/26)	20% $n = 4/20$	All current IDUs
Tiffen and Sheridan, 2002[73]			63% before intervention, 89% after intervention	This study looks at the impact of a care-coordinator explaining the purpose of referral $n = 11$
Reported in Bird *et al*., 2001[30]	Survey in the Grampian region, Scotland	42% (260/613)		No data on risk factor provided

DAU, drug and alcohol unit.

An unpublished study by Irving and colleagues gives estimates of attendance at specialist clinics by source of original referral (Irving WL, University of Nottingham: personal communication, 2005). The overall value from this study (39%) for acceptance of PCR testing is used in the general case (48.8% of those with a positive ELISA test were referred for specialist management, of whom 79.8% attended). These data have the advantage of combining referral and attendance rates and of being the most up-to-date estimate available.

Liver biopsy

Samples testing positive on PCR are genotyped to consider the need for biopsy. Until recently, liver biopsy was recommended in all cases as treatment was reserved for people with moderate to severe non-cirrhotic disease only. However, more recent protocols recommend proceeding to treatment without biopsy in patients with genotypes 2 and 3 given the high likelihood of treatment success in these subgroups (Main J, Imperial College, London: personal communication, 2005; Cramp ME, Derriford Hospital, Plymouth: personal communication, 2004). Very recently, treatment of cases with mild liver disease has been shown to be beneficial and cost-effective where infection is with genotype 2 or 3.[45] Biopsy might still be considered in cases with genotype 2 or 3 where cirrhosis is suspected, as monitoring for the development of HCC may be indicated. Biopsy for this purpose is not included in the model, nor is the accuracy of histological classification following biopsy. A small risk of death (3 per 10000) following biopsy has been incorporated,[74] although the risk and impact of other serious complications such as pain, pneumothorax and haemothorax, which are rare, are not incorporated. These assumptions may result in a very small bias in favour of case-finding.

Acceptance of liver biopsy

Patients may not attend for liver biopsy, in which case they will not proceed to treatment and will follow the natural history of infection. Data on biopsy uptake come mainly from the studies described above in which uptake of PCR is documented (*Table 7*). A value of 89.6% was used for acceptance of liver biopsy. This was taken from the unpublished study by Irving and colleagues in Nottingham described above and has the advantages of being the most up to date estimate available and excluding people who would not be

TABLE 7 *Acceptance of liver biopsy*

Study	Not offered biopsy since ineligible for treatment	Accept biopsy
Foster *et al.*,1997[75]		44% (46/104)
Irving (personal communication, 2005)	12.7% (7/55)	89.6% (43/48)
Jowett *et al.*, 2001[71]		77% (137/179)

eligible for treatment regardless of biopsy results. A range of acceptance rates were explored between 5 and 95% in the sensitivity analysis.

People who are lost to follow-up after testing or biopsy may re-present and be considered for treatment [see the section 'Spontaneous presentation for HCV testing and re-presentation after loss to follow-up' (p. 24)].

Interventions

The model considers two interventions for identified cases: (a) combination therapy with PegIFN and ribavirin and (b) harm reduction by advice to limit alcohol intake.

Combination therapy

Treatment of HCV infection has gone through, and continues to undergo, rapid change. Guidelines from the British Association for the Study of the Liver[37,68] and NICE Technology Appraisal Guidance[76] suggest that treatment should be restricted to people with moderate to severe disease, based on liver biopsy. However, NICE guidelines also state that it is reasonable to treat **symptomatic** patients even if they have only mild disease on the liver biopsy.[76] As noted above, recent research suggests that liver biopsy is not necessary to inform treatment decisions in cases with genotype 2 or 3. Although widely accepted, this has not yet been reflected in national professional or NHS guidelines. In order to reflect what we believe will become standard practice in the management of HCV in the near future, treatment of mild hepatitis C (according to genotype) was modelled and treatment of people found to have cirrhosis at presentation included (Main J, Imperial College, London: personal communication, 2005; Cramp ME, Derriford Hospital, Plymouth: personal communication, 2004).

Treatment is with PegIFN at standard doses combined with ribavirin. All patients receive treatment for 48 weeks. The authors chose to use this treatment duration as data for treatment effectiveness and associated costs and utilities are derived from RCTs in which treatment was administered for 48 weeks. Current UK guidelines suggest that patients with genotype 2 or 3 should receive treatment for 24 weeks. Patients with genotype 1 or 4 who do not show a treatment response (on quantitative PCR) after 12 weeks of treatment may also have their treatment terminated early. This assumption may bias slightly against case-finding.

Treatment is based on genotype and histology. Patients with genotype 2 or 3 or cirrhosis proceed directly to treatment whereas those with genotype 1 are staged using biopsy. People with genotype 1 (or 4) and moderate disease are treated. Those with genotype 1 (or 4) and mild disease are observed and may receive treatment if they progress to moderate hepatitis and meet other eligibility criteria.

No early stopping rules are employed in the treatment of patients with genotype 1 (or 4). Side-effects are modelled through application of utility decrements during the treatment cycles, based on data from the HTA Mild HCV Trial [see the section 'Utility values' (p. 34)].

The authors have not considered IFN monotherapy as antiviral therapy, which may be required in a minority of people who cannot tolerate ribavirin.

Eligibility for treatment

Eligibility criteria are reported in detail in the section 'Drug therapy' (p. 5). Using data from a large audit of patients with newly diagnosed hepatitis C (Irving WL, University of Nottingham: personal communication, 2005), it was assumed that 12% of individuals have absolute contraindications to treatment and are therefore not offered further investigation. We chose to use these data because they represent a large UK study of patients with hepatitis C and provide the most up-to-date estimate available. No distinction is made between individuals who

TABLE 8 *Acceptance of treatment*

Study	Accept treatment	*N*
Foster *et al.*, 1997[75]	Mild: 22% (requested treatment) Moderate or severe: 55% Cirrhosis: 54%	13/59 33/60 21/39
Irving (personal communication, 2005)	60.5%	26/43
Reported in Bird *et al.*, 2001[30]	19%	32/170

TABLE 9 *Effectiveness of combination antiviral therapy for HCV using pegylated interferon (%)*

Outcome	Study		
	Manns *et al.*, 2001[43] (*N* = 511)	Fried *et al.*, 2002[44] (*N* = 453)	Pooled[42] (*N* = 964)
SVR, overall (ITT)	54	56	55
SVR, genotype 1 or 4 (ITT)	42	48	45
SVR, genotype 2 or 3 (ITT)	82	76	79
SVR, patients with cirrhosis (ITT)	44	43	44
Adherence to treatment	97	78	88
Genotype 1 or 4 (treatment completers)	43	61	50
Genotype 2 or 3 (treatment completers)	85	97	90
Cirrhosis (treatment completers)	45	55	48

ITT, intention-to-treat.

reach the point of consideration for treatment following systematic case-finding or spontaneous presentation.

Acceptance of treatment

Acceptance of treatment is not well documented in the available literature and the impact of changing indications for treatment on acceptance are not clear. The studies by Foster and colleagues[75] and Irving and colleagues (Irving W, University of Nottingham: personal communication, 2005) indicate that treatment is accepted in approximately 55–60% of patients (*Table 8*). Foster and colleagues report that similar proportions of people with and without cirrhosis accepted treatment and that 22% of people with mild disease requested treatment. An unpublished survey of gastroenterologists conducted in the Grampian Region (reported by Bird and colleagues[30]) suggested that only 19% of eligible patients received treatment.

Two treatment acceptance rates were used in the model. The figure reported by Irving and colleagues (60.5%) was used for patients with genotype 2 or 3. This is a combined figure for all disease severities as, in the model, all patients with genotype 2 or 3 are offered treatment regardless of severity. These data have the advantage of being the most up-to-date available and are collected in a UK setting. For patients with genotype 1 or 4 (patients with mild disease are not offered treatment) the data from the study by Foster and colleagues (55%) were used because, although this is a slightly older study, it is the only source to provide acceptance rates by disease severity.

It is not clear whether acceptance rates will change if indications for treatment extend to mild disease.

Response to treatment

Responses to combination therapy are modelled on the results of a systematic review of pegylated combination therapy carried out by Shepherd and colleagues to inform NICE guidance in 2004.[42] This is the most up-to-date estimate of treatment response available. Sustained viral response (SVR) is defined as the absence of detectable HCV RNA at 24 weeks after cessation of therapy and is assumed to indicate complete clearance of HCV. *Table 9* presents the results of the two key trials of pegylated combination therapy in moderate to severe hepatitis and cirrhosis and the pooled analysis carried out by Shepherd and colleagues.[42]

Because compliance is considered separately, the figures for treatment completers were used and response rates modelled for patients with

genotype 1 and 4 and genotype 2 and 3 separately. The data reported in the trials included patients with cirrhosis. In order to obtain a more accurate response rate for patients with mild, moderate and severe disease, the data were recalculated omitting patients with cirrhosis. Combining these figures with the disease severity mix in the modelled cohort, a combined SVR for all patients with genotype 1 or 4 of 54% and with genotype 2 or 3 of 94% was obtained. This reflects the small numbers of patients with genotype 1 and 4 who receive treatment, and emphasises that most patients who achieve an SVR have genotype 2 or 3.

It was assumed that these SVR rates are also achieved in patients with mild disease, as there are no empirical data available to inform this parameter based on treatment with **pegylated** IFN. Treatment response was not reported by genotype in patients with cirrhosis. It was also assumed that SVR will vary by genotype in cirrhosis and modelled an SVR of 48% in genotypes 2 and 3 and 24% in genotypes 1 and 4.

Patients who achieve an SVR do not show further progression of hepatitis [see the section 'Long-term consequences' (p. 19) for further details]. In the case of people with cirrhosis, it was assumed that no further progression occurs, that is, patients will not proceed to decompensated cirrhosis. However, they remain subject to the risk of progression to HCC.

Treatment completion rates are based on the pooled estimates reported in *Table 9* according to severity and genotype, using data for treatment completers applied at the end of the 48-week treatment period.

Patients who do not achieve an SVR are assumed to be at the same risk of progression as if they had not received treatment, that is, depending on time since past infection and other subgroup characteristics as described in the section 'Long-term consequences' (p. 19).

It was assumed that patients who do not complete treatment do not obtain a response, that is, that response is only possible after all four cycles of treatment are completed, with associated costs. In fact, some patients who do not complete therapy may show a response in the model, but estimates for this probability are not available. This may introduce a small bias against case-finding since cases which achieve a response despite incomplete adherence will contribute to cumulative costs but not to cumulative benefits.

Alcohol harm reduction

In the previous HTA,[29] it was assumed that people would be offered testing only if they would be eligible for combination therapy. However, arguments might be made for testing IDUs regardless of antiviral treatment eligibility:

- intrinsic value of information on health status
- reducing risk of infection in others through avoidance of risky behaviours
- slowing progression of HCV disease by reducing alcohol intake.

Based on a systematic review, the last assessment showed that there was little evidence on which to assume that risky behaviours would be reduced as a result of learning HCV status, although the evidence base was very small at that time. The potential for health gain through this route is greater in current injectors than those who are no longer injecting, which is beyond the scope of this assessment. Nevertheless, some reduction in spread of HCV might result from changes in behaviour recommended in current guidelines (e.g. barrier contraception in people with multiple partners). These issues are not considered in the current model, which does not consider infection transmission in the population, that is, the perspective of the model is restricted to individuals who are already infected. The impact of reduced alcohol intake is therefore included as a mechanism by which case-finding might demonstrate benefits beyond those of combination therapy in eligible people in the IDU population.

The impact of alcohol as a co-factor in disease progression with HCV is described in the section 'Long-term consequences' (p. 19). The model uses the long-term progression data synthesised by Freeman and colleagues, in which alcohol use was defined using a binary variable of more or less than 50 g/day.[6] This carries a relative risk of progression to cirrhosis of 1.61.[6] Hutchinson and colleagues, in an unpublished study of the epidemiology of HCV in Glasgow, reported that 40% of former IDUs have high alcohol intake (Hutchinson S, University of Strathclyde: personal communication, 2005). It was assumed that the definitions of high alcohol intake by Hutchinson and colleagues and Freeman and colleagues are equivalent.

The effect of excessive alcohol consumption is incorporated in the model through a hazard

TABLE 10 *Cumulative disease progression rates (%)*

	Without excessive alcohol intake	With excessive alcohol intake
Mild to moderate	11.04	13.16
Moderate to severe	13.36	15.88
Severe to cirrhosis	15.45	18.33

coefficient for disease progression. The cumulative rates for progression after 10 years of infection with and without the effect of excessive alcohol intake are shown in *Table 10*.

The effectiveness of a brief intervention to reduce alcohol consumption was estimated from a recent, good-quality systematic review based in general practices.[77] In the absence of data on a more specific population, it was assumed that effectiveness would be unchanged in people with a history of IDU and HCV infection. The pooled estimate for the effectiveness of brief interventions, modelled as requiring an additional consultation with a nurse or counsellor, is for an absolute risk reduction of 10.5% in the proportion of people drinking more than sensible limits. This equates to a relative risk reduction of 35.4%. This figure is used to adjust the prevalence of people drinking more than sensible limits in the model (50 g/day). A brief intervention is costed as a single counselling session, provided by a non-specialist, costing £22, and is applied only in the case-finding arm. The model is run with and without this factor to demonstrate the contribution of alcohol reduction.

Long-term consequences

Overview

This section gives an overview of how long-term disease is modelled. The events incorporated in the long-term disease progression element of the model are summarised in *Figure 2*. Subsequent sections describe assumptions made on progression and clinical management in more detail. The costs and QoL associated with each state are described separately in the sections 'Costs' (p. 31) and 'Utility values' (p. 34).

The long-term model follows two cohorts: those in whom systematic case-finding is applied and those who are only diagnosed if they present spontaneously for testing. In both cohorts, the underlying prevalence of HCV is presumed [see the section 'Population characteristics (p. 11)]. Progression is determined using long-term data on risk from longitudinal studies of people with HCV, adjusted to estimate probabilities of moving between states in the 3-month cycle of the model. Cost and QALYs for each cohort are estimated from the total time spent in each state.

Patients are categorised according to whether their condition is diagnosed or undiagnosed (i.e. in response to systematic case-finding or spontaneous presentation) and whether they have been treated or not. Importantly, people in the non-case-finding cohort may present for testing spontaneously and those who refuse testing in the case-finding cohort may re-present later. Details of the assumptions around spontaneous presentation are given in the section 'Spontaneous presentation for HCV testing and re-presentation after loss to follow-up' (p. 24).

People who have not been treated, or who do not achieve a response to treatment, are subject to the probabilities of progressing through the states shown in *Figure 2*.

Progression through mild, moderate and severe hepatitis is assumed to be sequential and linear. Patients who develop cirrhosis are then at risk of developing HCC or decompensated cirrhosis. Decompensated cirrhosis is modelled as a single state, subsuming ascites, hepatic encephalopathy and oesophageal varices.

Liver transplantation may be considered in people with decompensated cirrhosis or HCC. Time is spent waiting for transplant. Following liver transplant, infection of the graft is assumed to occur and this may lead to cirrhosis, decompensation or HCC. A second transplant may be considered. Following transplant, progression to decompensation only was modelled and the cost of decompensation was inflated to take a second transplantation into account. Use of antiviral therapy after liver transplant has not been modelled.

People may die in any of the states in the long-term progression element of the model. Mortality may be from disease-specific causes (such as

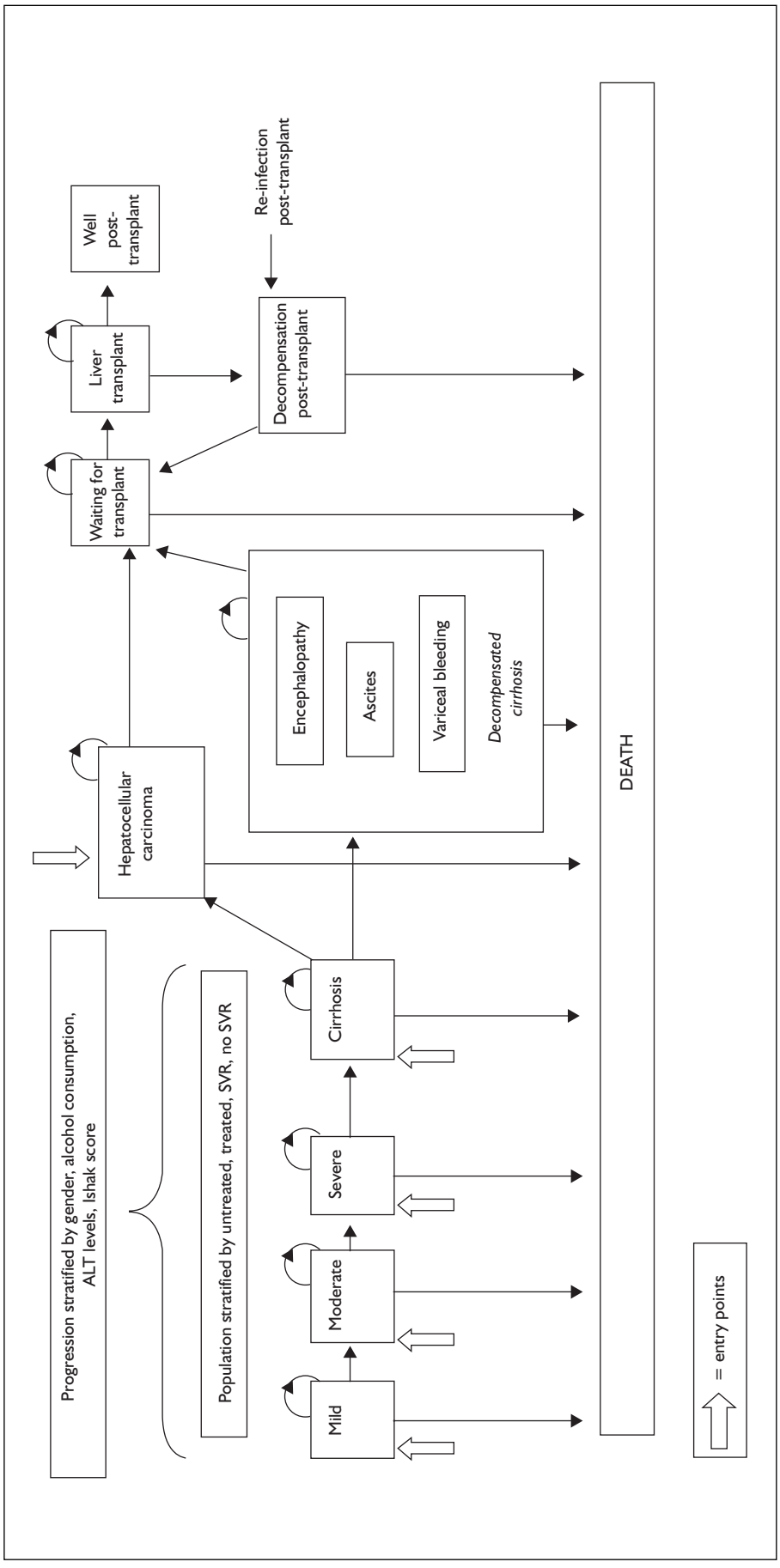


FIGURE 2 *Long-term disease progression*

TABLE 11 *Prevalence of risk factors for progression to cirrhosis*

Risk factor	Estimate for the model	Notes	Source
Gender	0.7	Assumed 70% of infected with HCV are males	Hutchinson *et al*. (Hutchinson, personal communication, 2005)
Alcohol consumption	0.4	Data from Glasgow	Hutchinson *et al*. (Hutchinson, personal communication, 2005)
Raised ALT	Mild 0.57 (SE 0.03) Moderate 0.82 (SE 0.034) Severe 0.83 (SE 0.042)	A review of community-based cohorts reports this proportion as 62%[79]	Trent HCV Study Cohort Database (Irving, personal communication, 2004)

SE, standard error.

decompensated cirrhosis or HCC) or from other causes (i.e. 'background' mortality).

People who have been treated and show a response are not subject to progression of hepatitis and their QoL (utility) improves. It was assumed that their degree of improvement in quality of life is equal to that reported in the HTA Mild HCV Trial.[78] However, it is unclear whether this is equivalent to that of people who are not infected with HCV [see the section 'Utility values' (p. 34)]. People who are treated in cirrhosis experience no further progression and are not at risk of decompensation. Their QoL returns to that of people who are not infected and their life expectancy, in the base case, is that of the general population at the same age. However, they remain at risk of developing HCC and are monitored for the development of HCC with annual ultrasound examination and specialist consultation [see the section 'Costs' (p. 31) for details of assumptions regarding costs].

Progression to cirrhosis

Progression through mild to moderate and severe hepatitis to cirrhosis was modelled using data from a good-quality systematic review of studies of progression, published in 2003 by Freeman and colleagues.[6,52] Disease severity was categorised as mild, moderate and severe based on HAI score, assuming a score of 3 for mild, 8 for moderate and 11 for severe disease.

Freeman and colleagues synthesised evidence from a range of settings to develop regression models for time to development of cirrhosis. Risk of cirrhosis was shown to be a function of time since infection, gender, alcohol consumption (below versus equal to or above 50 g/day), alanine aminotransferase (ALT) levels and degree of liver inflammation (based on HAI score). The coefficients for each of these factors in the Freeman model were used to stratify the model.

Risk of progression was estimated for each 3-month cycle in our model from the cumulative risk derived from the function described by Freeman and colleagues. This is converted into a transition probability using the equation

$$p = 1 - e^{-rt}$$

where r is the rate and t is an indicator of time since infection (in this case based on age) In order to use the Freeman regression model, it was necessary to estimate the prevalence of risk factors in former IDUs in the UK. *Table 11* reports the values used. Data from a large community study in Glasgow were used for estimates of gender and proportion of people with increased alcohol use (Hutchinson S, University of Strathclyde: personal communication, 2005).

Primary data from the Trent HCV Study Cohort Database were used to estimate the prevalence of elevated ALT levels in people with IDU and HCV infection by histological severity at presentation. Average ALT levels for each individual were transformed into a binary variable with the cut-off for defining abnormality set as 50 units/l.

Table 12 shows the cumulative risks of progression to the next stage in the development of HCV disease. These were estimated by applying the Freeman regression model and prevalences shown in *Table 11* to estimate progression to cirrhosis. It was then assumed that progression between mild, moderate and severe hepatitis occurs at a constant rate within each histological category and that progression is sequential, that is, individuals proceed from mild to moderate and from moderate to severe, but cannot proceed from mild to severe directly. Resolution of hepatitis (e.g. moving from moderate to mild disease) is not modelled.

TABLE 12 *Progression of HCV disease.*

Progression		Cumulative risk, tested individuals who also receive alcohol advice (%)		Cumulative risk, untested individuals, no alcohol advice (%)	
		20 years[a]	30 years[a]	20 years[a]	30 years[a]
Mild to moderate hepatitis					
	All	6.19	12.08	6.20	12.10
	Male	6.31	12.31	6.32	12.33
	Female	5.93	11.60	5.94	11.62
Moderate to severe hepatitis					
	All	7.52	14.59	7.54	14.62
	Male	7.67	14.87	7.68	14.89
	Female	7.22	14.03	7.23	14.05
Severe hepatitis to cirrhosis					
	All	8.75	16.87	8.77	16.90
	Male	8.92	17.18	8.94	17.21
	Female	8.40	16.22	8.42	16.25

[a]At 20 and 30 years past infections

The model of progression is not based on data specific to the IDU population, nor does it take account of factors which influence the effectiveness of combination therapy, such as genotype and viral load. However, Freeman and colleagues and others have shown that source of infection, genotype and viral load are not significant independent risk factors for progression.[6,52,70,80]

Decompensated cirrhosis

Decompensated cirrhosis refers to any of three specific conditions which may develop in advanced liver failure: ascites, oesophageal varices or hepatic encephalopathy. There is likely to be correlation between the states. No data were found to allow separate decompensated states with the appropriate correlation between them to be modelled and ignoring the correlation may result in important bias.

The model therefore combines the three conditions into a single state. This approach simplifies clinical progression and may appear somewhat unrealistic. However, it has the important advantage that the correlation between the three manifestations of decompensation (in terms of risk of occurrence, cost and QoL) need not be considered. In addition, recent estimates have become available on the overall risk of progression to any decompensated state and on the associated costs and QoL.[78] These were the only appropriate data that could be identified and were therefore used in the model. Progression from cirrhosis to decompensation is modelled at a constant rate of 5.8% per year.

Hepatocellular carcinoma

Published estimates on the incidence of HCC vary (*Table 13*). Although all included patients with cirrhosis, in two studies the cohort studied was much larger and included a small subset of patients with cirrhosis.[12,81] Studies included between 103 and 416 people. Follow-up ranged from 40 to 84 months. Incidence of HCC among former IDUs is not reported separately in any study. However, development of HCC has not been shown to be associated with mode of infection.

Most studies report an annual incidence rate of between 2 and 4%. Severity of disease at inclusion, examination interval and inclusion of patients with heavy alcohol intake or history of interferon treatment[47] may account for some or all of the differences between reported incidence.[82] Previous models have used the data from Fattovich and colleagues (annual incidence of HCC of 1.4%/year).[83] However, detailed examination of the literature revealed several studies in which the incidence was higher than this (*Table 13*). It was authors therefore assumed an intermediate value for incidence of 2.5% for the general case and tested this over an interval of 1–5% in sensitivity analyses.

Liver transplantation

The probability of having a liver transplant in advanced liver failure is taken from UK national transplant statistics.[90] As HCV is now the leading cause of liver transplantation in the UK and the principle risk factor for contracting HCV is

TABLE 13 *Development of HCC in people with cirrhosis*

Study	Characteristics	Incidence
Fattovitch *et al*., 1997[83,84]	*N* = 384 53.5% treated with IFN Follow-up 61 months	1.4% per year
Fattovitch *et al*., 2002[85]	*N* = 136 Untreated with IFN Follow-up 79 months	10% at 5 years
Benvegnu and Alberti, 2001[86]	*N* = 284 IFN treatment unknown Follow-up 84 months	2% per year (years 1–5) 4% per year (years 5–10)
Bruno *et al*., 1997[87]	*N* = 163 IFN treatment unknown Follow-up 68 months	2.5% of study population developed HCC, rate not given
Serfaty *et al*., 1998[88]	*N* = 103 57% treated with IFN Follow-up 40 months	3.3% per year (1.8% at 2 years in treated patients, 5% at 2 years in untreated patients)
Degos *et al*., 2000[89]	*N* = 416 54% treated with IFN Follow-up 68 months	13.4% at 5 years
Roffi *et al*., 2001[12]	*N* = 280 with cirrhosis, part of cohort of 2307 people with HCV 43% treated with IFN Follow-up 64 months	4.1 per 100 person-years
Niederau *et al*., 1998[81]	*N* = 141 with cirrhosis, part of cohort of 838 people with HCV 52% of whole cohort treated with IFN Follow-up 50 months	11.3% of study population developed HCC, rate not given

injecting drug use, it was assumed that all liver transplants in the UK are performed in patients with HCV and that all these individuals contracted HCV as a result of injecting drug use. It was also assumed that 7% of individuals are at risk of getting on the waiting list for a transplant and that 73% of these will receive a transplant. The annual probability of first liver transplantation is therefore 5%.

Infection of the transplant graft has been reported as occurring in almost all patients eventually.[91] Post-transplant states were modelled very simply using two states: healthy post-transplant and progression to decompensated cirrhosis in the graft. Progression is believed to occur more aggressively after transplant (*Table 14*). In a review of the natural history of HCV after transplant,[91] the probability of developing cirrhosis after transplant is estimated to reach 30% at 5 years. Two studies conducted in Europe[49,92] report rates of 14% over 2 years and 16% over 2.8 years. In transplanted patients with cirrhosis, the risk of decompensation is 62% over 3 years.[91] These estimates were combined and a fixed rate (i.e. not increasing with time since transplantation) of progression to decompensation in transplanted patients of 6.9% per year used.

Mortality

Two types of mortality rate are included in the model:

1. State specific mortality (*Table 15*)
   (a) Liver biopsy
   (b) Decompensated cirrhosis
   (c) Hepatocellular carcinoma
   (d) Post-transplant.
2. Age- and sex-specific mortality from all other causes based on UK life tables.

It has been assumed that deaths from cirrhosis are driven by its complications (that is decompensated cirrhosis and HCC) and no independent risk is applied to this state.

Background mortality refers to deaths from all causes not otherwise included in the model. This

TABLE 14 *Progression following transplant*

Progression to	Source	Incidence
Cirrhosis	Rodriguez-Luna and Douglas, 2004[91] (summary of 7 studies)	30% at 5 years
	Testa *et al*., 2000[49] *N* = 300	14% of patients developed cirrhosis within 2 years
	Neumann *et al.*, 2004[92] *N* = 183	16% of patients developed cirrhosis within 2.8 years
Decompensation	Rodriguez-Luna and Douglas, 2004[91] (summary of 3 studies)	42% over 3 years

TABLE 15 *Mortality rates*

State	Death rates, per year	Source and notes
Mortality with biopsy	0.3%	
Decompensated cirrhosis	49.2% at 5 years	Planas *et al*., 2004.[93] *N* = 200, follow-up 34 months. Note a similar proportion (50%) is reported in Fattovitch *et al*., 1997.[83]
HCC	91%	Cancer Registry survival data, 2004.[94] Age-standardised relative survival
Longer-term mortality after transplant	31.2% at 10 years	Neumann *et al*., 2004.[92] *N* = 183, follow-up 59 months
Background mortality, i.e. all other causes of death	Variable – by age and sex	National Mortality statistics (Series DH2), 2004[95]
		Dependent on age of cohort. Excluding liver disease and liver cancer, limited to ICD-10 C22.0 Liver cell carcinoma, C22.9 Liver, unspecified and ICD-10 K70 to K77, diseases of the liver, i.e. cirrhosis-related

was calculated from general population data routinely reported by the Office of National Statistics. Causes of death are reported using the International Classification of Disease (ICD-10). Mortality was modelled for all causes, by age and sex, with the following excluded: liver disease and liver cancer (limited to ICD-10 C22.0 liver cell carcinoma, C22.9 Liver, unspecified and K70 to K77, Diseases of the liver, i.e. cirrhosis-related). All other types of liver cancer were assumed not to be related to HCV infection. Background mortality is time dependent, that is, as the cohorts age, mortality increases appropriately.

Life expectancy in individuals with a history of past injecting drug use is unknown. In the general case, the background force of mortality was assumed to be the same as the general population. Increased mortality is explored in sensitivity analyses.

Spontaneous presentation for HCV testing and re-presentation after loss to follow-up

An important limitation of the previous model was the simplified approach to diagnosis in the comparator arm, that is, testing at the request of the patient. In the previous model it was assumed that presentation would occur, on average, 10 years later in the absence of systematic case-finding. Furthermore, it was assumed that people who initially refused testing, biopsy or treatment would not return for testing at some later date.

In this analysis, a more sophisticated approach was taken to this parameter. First, it was assumed that people in the non-case-finding cohort will present for testing throughout the course of the model. This may be in response to the development of symptoms or because of anxiety about potential infection that, in turn, may relate to increasing

societal awareness of HCV and its relationship with a history of injecting drug use. This is referred to as spontaneous presentation.

Second, in the case-finding arm, people who are offered but do not take up testing, may present later. This referred to as re-presentation.

This element of the model is important for several reasons:

- A large proportion of people are lost to follow-up during investigation and treatment, so the initial yield of case-finding is low.
- The model takes a long-term perspective and so the impact of spontaneous presentation and re-presentation has, over time, a major impact.
- There is no evidence on which to base assumptions regarding re-presentation.

It is difficult to determine the number of individuals who present spontaneously for HCV testing in the UK. Although available data on the diagnosis of HCV will include some individuals who have presented spontaneously and some who have been identified through case-finding strategies [see the section 'Current status of case-finding in the UK (p. 4)], current data on presentation were used as the basis for this parameter.

The proportion of individuals presenting spontaneously was approximated as follows. In the general case, it was assumed that all cases currently diagnosed in the UK come forward for testing spontaneously, recognising that this introduces a bias against case-finding. Since the model assumes an underlying and known prevalence, an estimate is needed of (a) the number of people who are currently undiagnosed and (b) the proportion of these people who present annually.

Bird and colleagues estimated the total number of cases of HCV in the UK.[23,30] Based on their study in Scotland (Hutchinson S, University of Strathclyde: personal communication, 2005), it was assumed that 70% of all cases are currently undiagnosed. The total number of notified diagnoses of HCV infection in England and Wales in 2003 was 6495.[31]

Using this method, the probability of spontaneous presentation is approximately 3.8% per year.

This probability is applied to people in the non-case-finding arm throughout the course of the model. It was also assumed that people who are tested but lost to follow-up may re-present at some point later. In the general case analysis, a positive effect of case-finding on the probability of re-presentation was assumed and this was modelled as double the spontaneous presentation rate (i.e. 7.7% per year).

Owing to the potential importance of this parameter and the uncertainty surrounding these assumptions, the impact of different hypotheses regarding the probability of spontaneous presentation or re-presentation in sensitivity analyses was considered [see the section 'Exploration of assumption around spontaneous rates of presentation' (p. 52)].

First, a scenario was taken in which there is a short-term increase in re-presentation rates in the case-finding arm. It was assumed that, for the first 2 years, the probability of re-presentation is twice that of spontaneous presentation (7.7%) in people who initially refuse the offer of an ELISA test. After this, the rate of re-presentation returns to the same as spontaneous presentation in the non-case-finding arm (3.8%). The probability of spontaneous presentation in the non-case-finding arm remains constant throughout the course of the model.

Scenarios were also explored in which rates of spontaneous and re-presentation of 2.5, 5, 7.5 and 10% are used. Finally, a situation was considered where there is no spontaneous or re-presentation in either arm of the model.

Case-finding strategies in different settings

Approaches were considered to case-finding in three settings: prison, drug and alcohol services and general practice. Other potential settings in which testing might be offered include pharmacies and NHS walk-in centres. However, owing to the lack of primary data available, it was impractical to explore these further. In some settings the demarcation between former and current injecting drug use is not always clear, and it is likely that current and former IDUs would be offered testing, although treatment is not offered to people who continue to inject. Both current and former IDUs in the target population were therefore included.

Case-finding in prisons

Based on two published reports of HCV testing programmes in prisons in the UK,[32,33] slightly different scenarios were developed for case-finding in prisons. The target population is all new

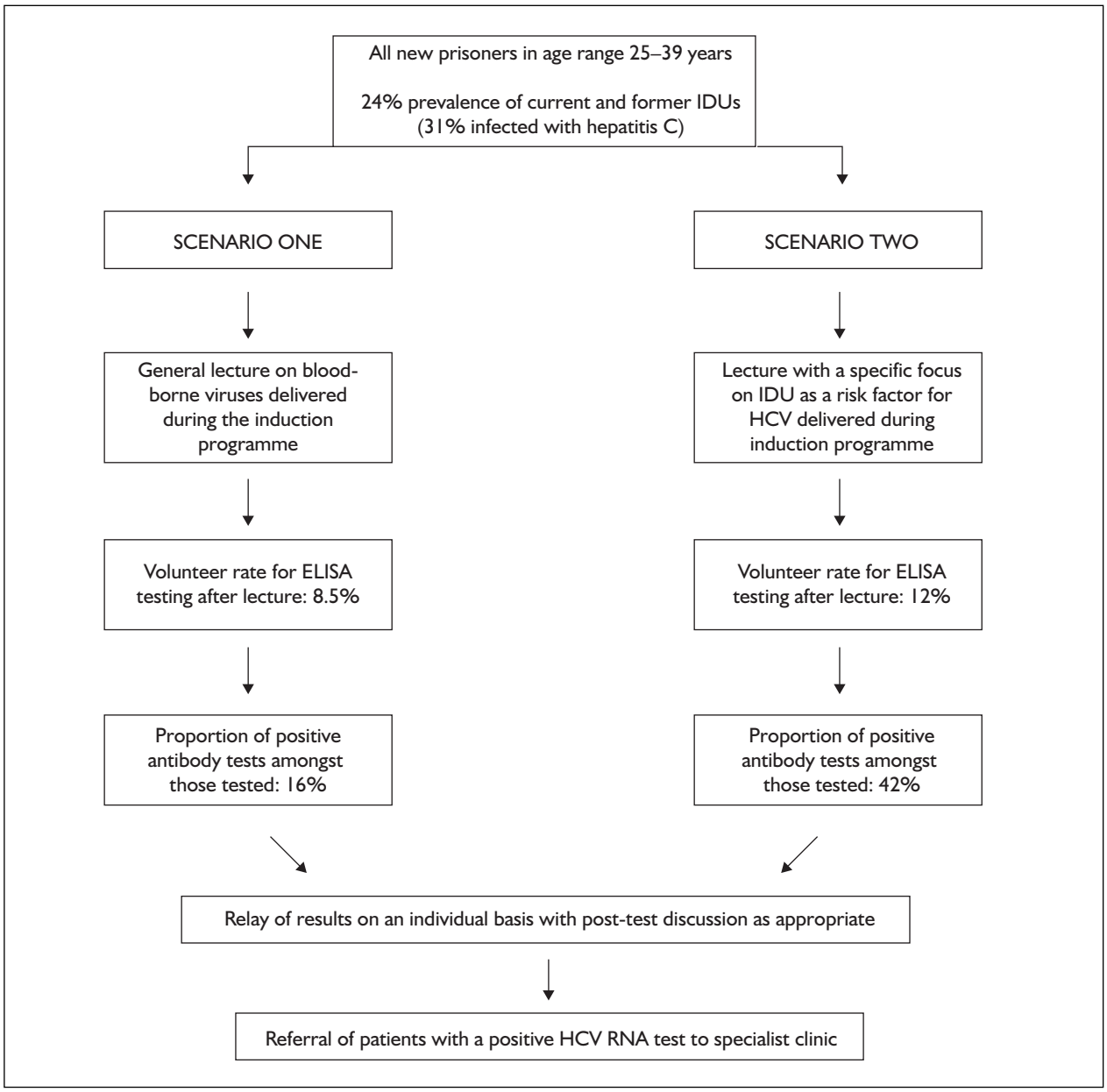


FIGURE 3 *Case-finding in prisons*

prisoners entering a prison within the target age range of 25–39 years. Home Office statistics indicate that 48% of the prison population in the UK is in this age group.[96] Based on the unlinked anonymous national survey of HCV prevalence in prisons in England and Wales conducted in 1997, it was estimated that within this population, 24% will have a history of current or former injecting drug use and that 31% of those will be infected with HCV.[64]

A similar approach to case-finding was described in both published reports; a lecture is delivered during the induction programme for new prisoners. Also, a similar number of prisoners volunteered for testing in each situation: 8.5 and 12%.[32,33] However, the number of positive ELISA tests arising from this encounter differed: 16% in Dartmoor[32] and 42% in the Isle of Wight.[32] The reason for this difference is not clear, but could be due to differences in the prevalence of injecting drug use, the prevalence of hepatitis C infection or, as seems more likely, the emphasis given to injecting drug use as a risk factor during the two lectures. The proportion of those tested with a history of injecting drug use in the Isle of Wight was 96%. This information is not provided in the report from Dartmoor prison. These figures were

TABLE 16 *Possible approaches to patient identification within general practice*

Approach	Description and notes
1. Offer counselling/test (by leaflet) to all adults in target age group attending for non-urgent appointment	Leaflet handed to patients by someone with an explanation that they fit the target age group and that the practice is running an HCV case-finding campaign Patient asked to make a further appointment to discuss if interested Relies on patient to read leaflet and be motivated to make further appointment Minimal time input, no expertise needed to distribute leaflets Age is only selecting characteristic, may not be efficient in low prevalence areas
2. Offer counselling/test (in person) to all adults in target age group attending for non-urgent appointment	Doctor/nurse offers counselling and test in all appropriate consultations Patient asked to make a further appointment to discuss if interested Some patients may be offended by the offer of a test Age is only selecting characteristic, may not be efficient in low prevalence areas
3. Questionnaire to all adult patients in practice (in person) to identify those with an IDU risk factor	Completed questionnaires analysed to determine 'at-risk' population 'At-risk' population offered opportunity to make appointment to discuss further if interested Opportunity to update database with other information at the same time Data are captured for future attempts at encouraging patients to come forward for testing if not interested this time Time consuming Response rates may be influenced by educational status and so increase inequalities in access to treatment
4. Questionnaire to all adult patients within the practice (by post) to identify those with an IDU risk factor	As above Will not pick up people with no fixed address Relies on patient to complete and return questionnaire, response rate may be low
5. Awareness campaign in practice	High-profile awareness campaign for limited period Patients' attention drawn to campaign by receptionist Patients routinely offered opportunity for counselling/testing during all non-urgent appointment with nurse/doctor
6. Database search to identify people with IDU as a risk factor	May not yield many patients if these data are not routinely collected by the practice
7. Offer counselling/test to all new patients joining a practice	Incorporate into new patient checks Will only identify those who change practice
8. Offer counselling/test within existing nurse-led clinics, e.g. well-woman, well-man	Patient asked to make additional appointment for further discussion if interested Efficiency of strategy may be increased if nurse already has rapport with patient
9. Target offer of counselling/test to mothers with young children within a practice	Mothers with young children are more likely to be accessing services and may provide an opportunity to access men (fathers) who are less likely to be in contact with general practice

used as the basis for two scenarios, which differ in the proportion of positive tests, assuming that this is due to the type of lecture provided (*Figure 3*).

As part of the induction programme, all new prisoners are provided with information on blood-borne viruses, including HCV, by a prison officer, on a group basis. The number of patients per group is based on the experience at Dartmoor prison: an average of 10 patients at each induction session. As part of the lecture, prisoners are offered the opportunity to make an appointment for individual discussion and a confidential test. Interested prisoners undergo a pre-test discussion and a blood sample is obtained for the initial ELISA test. Results of the ELISA test are relayed to prisoners on an individual basis with post-test discussion as required. All prisoners are counselled on harm minimisation with respect to alcohol consumption and injecting drug use and those with a positive HCV RNA result are referred for further investigation and, where appropriate, treatment.

Case-finding in general practice

No published examples of case-finding were found for HCV in general practices in England and Wales. One unpublished example of a population-based approach in Scotland was identified through contact with experts. There are many possible

approaches to identifying patients who might be offered HCV testing in general practice. In the absence of any descriptions of existing approaches, a range of possible approaches was developed in consultation with clinical experts (*Table 16*).

As it was impractical to explore all these scenarios, two were chosen as the basis for evaluation: (1) targeting patients already recorded as having a history of IDU and (2) a general population approach (*Figure 4*). The first scenario was chosen on the basis of analogy with policies for preventing coronary heart disease in general practice, where the first objective has been to maximise treatment to reduce risk in people known to services and at highest risk (i.e. people with existing disease). The second approach was chosen because the only study of case-finding in general practice in the UK took this approach and offering testing to all patients in the practice may be the only way of reaching the 'hidden population' who have injected drugs in the past, perhaps on only a few occasions, but who do not currently misuse drugs.

Targeting IDUs
In this scenario, all patients with a history of current or former injecting drug use would be identified from patient records, probably using a combination of clinical history and treatment codes.

A letter from the patient's GP would be sent to each patient along with an information leaflet describing the risk factors for contracting hepatitis C. Interested patients would be invited to make an appointment with a nurse counsellor for further discussion of testing. Manual and computer practice records would be flagged.

The estimates of the proportion of the target group that might volunteer for testing (49%) is taken from a study of testing for hepatitis C within a drug and alcohol service in 1997 as data from within general practice are not available.[70] The proportion with a positive antibody test will depend on the prevalence of HCV amongst IDUs in the local area. A prevalence of 49% was used, as described in the section 'Prevalence of HCV' (p. 11).

General population approach
This scenario is based on a study of case-finding carried out recently in a Scottish general practice in an area of high deprivation and presumed HCV prevalence (Anderson E, Department of Public Health, Lanarkshire NHS Board: personal communication, 2005). Counselling on HCV and ELISA testing was offered to all patients aged 30–54 years attending for a non-urgent appointment. The age group was chosen in an attempt to identify patients with an increased need for treatment given accepted indications at that time, that is, those who have been infected for sufficient duration to develop moderate hepatitis. Patients in this age group are also more likely to be former, as opposed to current, IDUs. About 50% of the target population (584/1165) attended the practice during the 6-month study period and ELISA tests were performed in 10% (n = 117) of the population. Fifteen patients (12.5% of those tested) had positive ELISA results. Of those with a positive test result,73% were aged between 30 and 39 years and 80% were male.

Following the above approach of Anderson and colleagues, it was assumed that literature on HCV is displayed in the surgery waiting room and a reminder displayed on the computer screen during each consultation, whether nurse or doctor led, with any patient in the target age range (30–54 years). Risk factors for hepatitis C are described using the literature provided and an appointment with the nurse counsellor would be made available for people who consider testing.

In both scenarios, all interested patients would receive a pre-test discussion and a blood sample is obtained. Results are reported to patients in a consultation with a post-test discussion as appropriate. Patients with a positive HCV RNA test are offered a referral to the specialist clinic for further investigation.

Case-finding in drug and alcohol services
There are very few published reports of case-finding approaches in drug and alcohol services in the UK, although the previous survey suggested that 26% of services in England offer testing for HCV. Anecdotally, a particular issue for community-based drug services is the provision of facilities for blood testing.

A study performed in rural south-east England considered opportunistic screening.[97] However, patients were required to give informed consent to take part in the study and it is not clear how many were excluded from this stage, limiting the value of this account. During a 12-month period, 102 patients were recruited into the study, 87 had injected drugs at some time during their lives and 34 continued to inject. Blood specimens were obtained from 89 (88.1%) patients, 86 were tested for HCV and 48 (56%) were antibody positive.

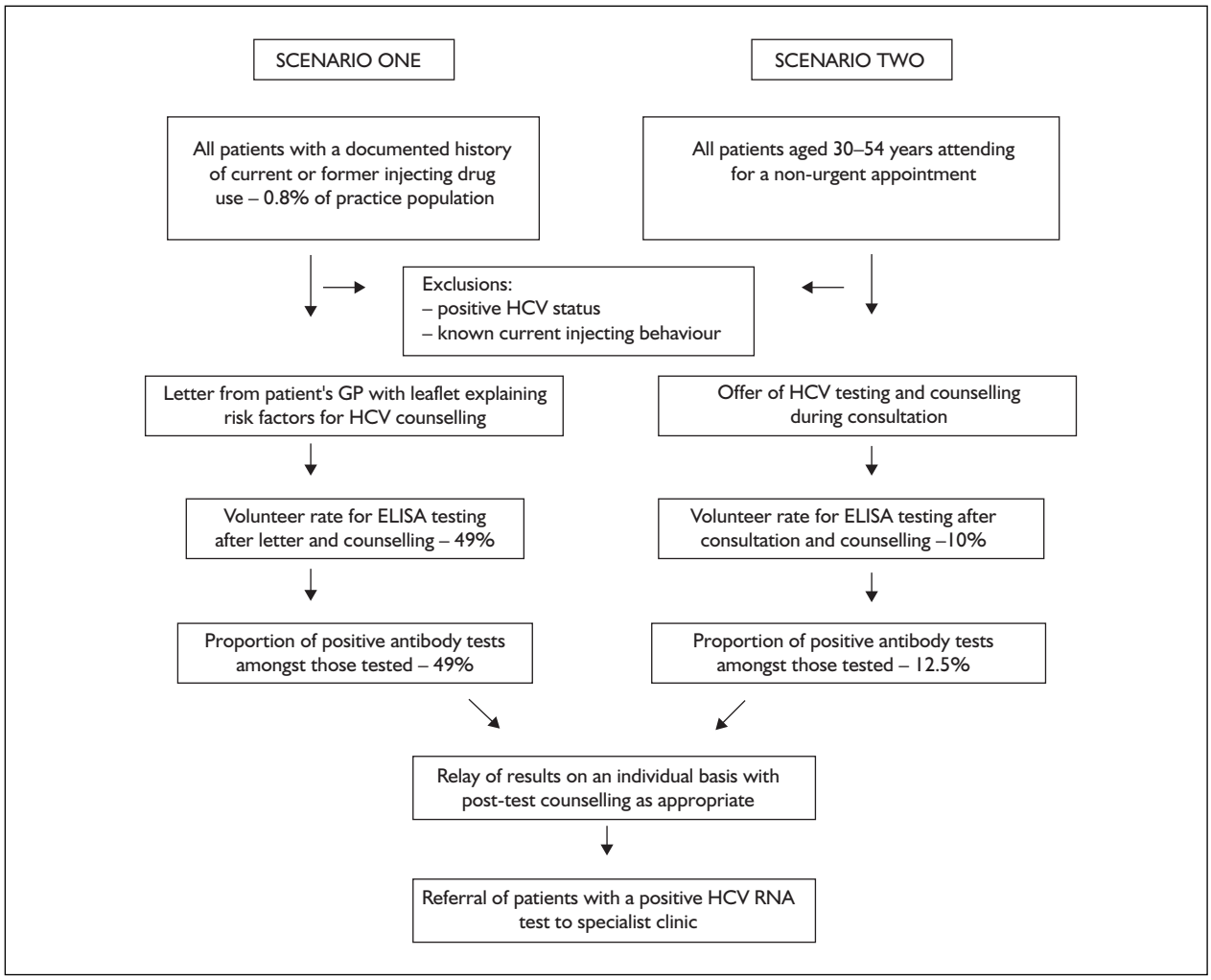


FIGURE 4 *Case-finding in general practice*

In another study, conducted in Newcastle, all people in contact with specialist drug services with a history of current or former injecting were offered counselling and testing for HCV.[70] Of the 1728 patients registered with the service, 202 (12%) had a history of current or former drug use and 98 of these (6%) were former injectors. Following counselling, 49% agreed to hepatitis C testing and 68% of these were antibody positive.

In Plymouth, the Drug and Alcohol Action Team employs a blood-borne viruses nurse whose primary objective is to provide hepatitis B vaccination to high-risk groups within the city, particularly those not in contact with general practice. Clients are also offered testing for HCV and HIV. Drug users are accessed in many places within the city, including homelessness shelters, drug services, massage parlours, the needle exchange and rehabilitation centres; uptake data are summarised in *Table 17* (Meachin C, Derriford Hospital, Plymouth: personal communication, 2005).

The study conducted in Newcastle and the experiences in Plymouth suggest that approximately half of those approached may take up the offer of an HCV test, therefore an acceptance of ELISA testing of 49% was used. The proportion of people with a positive antibody test will depend on the prevalence of HCV within the local area. A prevalence of 68% was used, as described in the study by Serfaty and colleagues.[70] Assumptions regarding resource use in this scenario are shown later in *Table 21*. These reports form the basis of a simple scenario for case-finding based in drug and alcohol services (*Figure 5*). All clients who are assessed by the blood-borne viruses nurse for hepatitis B vaccination are offered the opportunity for a discussion and testing for hepatitis C. Interested clients are offered counselling and a blood sample

TABLE 17 *Uptake of HCV testing by IDUs in Plymouth*

	Proportion of people
Acceptance of ELISA test	52% (99/192)
Positive ELISA test	23% (23/99)
Acceptance of PCR test	78% (18/23)
Positive PCR test	78% (14/18)
Referred for specialist management	93% (13/14)

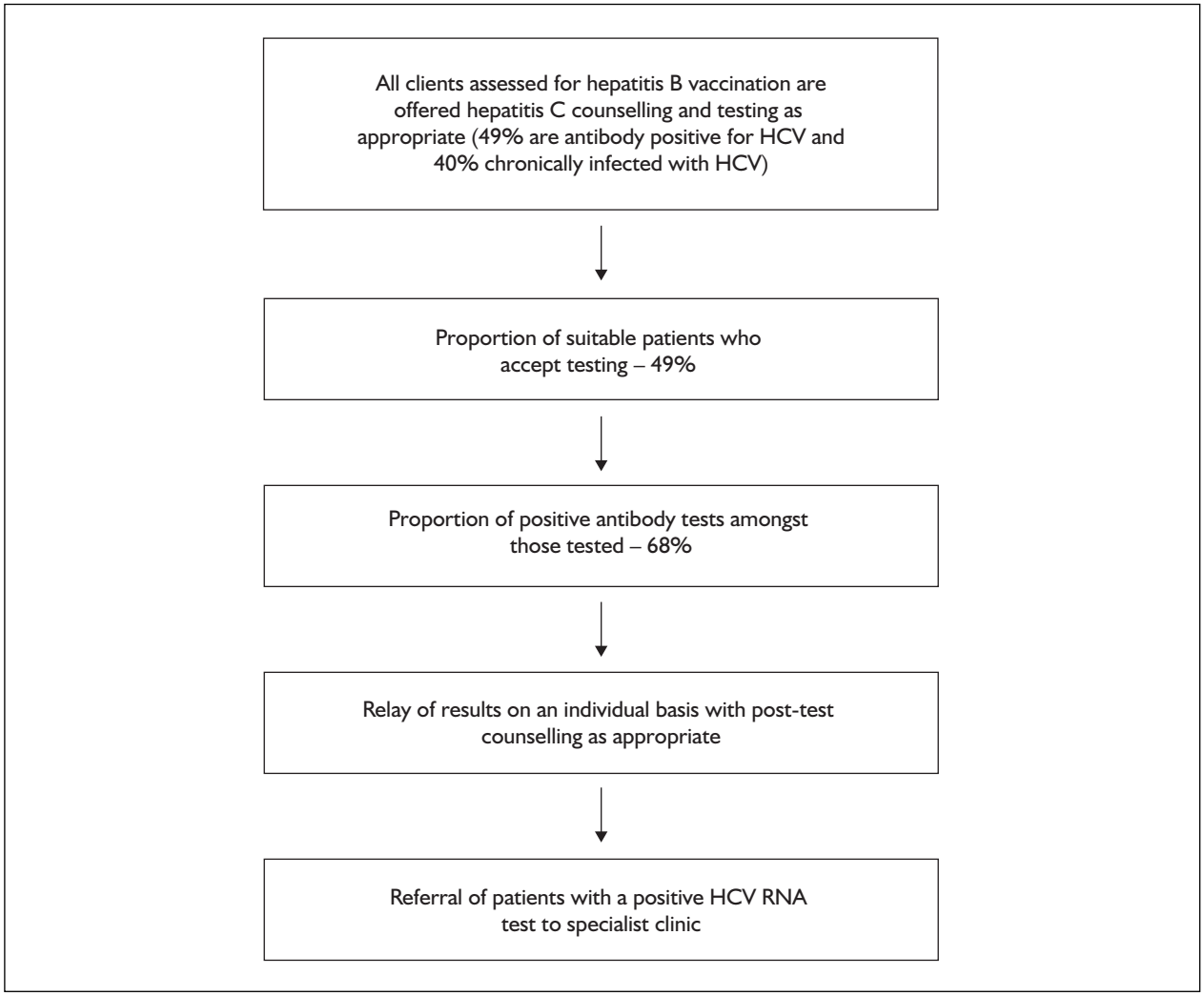


FIGURE 5 *Case-finding in drug and alcohol services*

is obtained for initial antibody testing. An appointment is arranged for face-to-face relay of results and a post-test discussion at a further dedicated session. Patients with a positive ELISA test are referred to specialist care for further investigation.

Table 18 summarises the main differences in data inputs between the various case-finding strategies. There are potentially large differences in the populations of patients accessed in the different settings which might impact on, for example, the proportion of individuals who receive notification of the test results and the proportion who are eligible for treatment. However, owing to the paucity of primary data available, setting-specific data were only applied to the prevalence of HCV within the population and the volunteer acceptance rate for testing. The average age of all individuals with a diagnosis of HCV is 37 years irrespective of the setting from which they were identified.

TABLE 18 *Summary of differences in data inputs between the general case and the different settings for case-finding*

Setting	ELISA acceptance rate (%)	Proportion of positive results (%)
General case	49	49
Prison scenario 1	8.5	16
Prison scenario 2	12	42
General practice, targeted approach	49	49
General practice, population approach	10	12.5
Drug and alcohol services	49	68

TABLE 19 *Testing and diagnosis costs*

Item	Cost (£)	SE (£)	Sources and notes
Cost of ELISA test	17	6.70	Mild HCV Trial[78]
Costs of communicating results, ELISA negative	2.70	0.27	Assuming one letter to patient and 5 minutes of nurse time to organise mail
Costs of counselling, communicating results, offer referral in ELISA positive individuals	30.70	3.70	One letter to patient + one GP visit to discuss results + cost of referral to specialist services[98]
Cost PCR	130	10.17	Assuming one ELISA test (£17, SE £6.70), one PCR test (£56, SE £10.17) and one specialist consultation (£57, SE £5.70)[98]
Cost of communicating result, PCR negative	2.70	0.27	Assuming one letter to patient and 5 minutes of nurse time to organise mail[98]
Cost of genotyping	94	10.10	Cost of test only[78]
Cost of offering liver biopsy to individuals who are genotype 1 or 4	57	5.70	Cost of one specialist consultation, counselling and referral[98]
Cost of counselling and communicating PCR results to individuals who are not eligible for treatment	109.25	10.93	Cost of consultation, cost of counselling and referral to consultation with Drug and Alcohol Services[98]
Cost of counselling and harm reduction advice	110.50	11.05	Consultation, cost of alcohol advice[98]
Cost of liver biopsy	249	11.37	
Cost of communicating non-eligibility for treatment, counselling on harm reduction after liver biopsy	79	7.90	Specialist consultation, cost of alcohol advice[98]
Cost of offering treatment (i.e. referral for treatment)	88.50	8.85	Consultation specialist and nurse appointment[98]

SE, standard error.

Costs

Testing and diagnosis costs

Resource use in the testing and diagnosis element of the model is summarised in *Table 19*. Costs were calculated by multiplying the resource use by estimates of unit costs for the base year (2004). Unit costs were obtained from two main sources: estimates published by the Personal and Social Services Research Unit (PSSRU) at the University of Kent[98] and the NHS R&D HTA funded RCT and cost-effectiveness model of combination therapy for mild HCV led by Wright and colleagues at St Mary's Hospital, London, and the London School of Hygiene and Tropical Medicine.[78] These are the best available sources of relevant cost information since they report recent UK data.

Estimates of the standard errors in cost measurements are required in order to carry out the probabilistic sensitivity analysis. Where these

TABLE 20 *Costs associated with disease states and combination therapy*

Disease state	Annual cost (SE) (£)[a]			
		Combination therapy	Sustained response	No response
Mild	138 (40)[b]	11,425[b]	259 (348)	118 (26)[b]
Moderate	717 (76)[b]	11,529[b]	717 (76)	730 (64)[b]
Severe	717 (76)	11,529[b]	717 (76)	717 (76)
Cirrhotic	1,138 (224)	11,938[b]	1,138 (224)	1,138 (224)
HCC	8,127 (1,910)			
Decompensated liver disease	9,120 (1,519)			
Waiting list for liver transplant	8,413 (930)			
Liver transplant	27,330 (2,885)			
Post-transplant, decompensated	9,458 (2,548)[c] 9,538 (inflated by costs of further transplants)			
Post-transplant, healthy	1,385 (355)			

SE, standard error.
[a] All cost data are taken from Wright and colleagues,[78] except for those in footnotes *b* and *c*.
[b] From Wright and colleagues,[78] PegIFN from the BNF.[99]
[c] From the Department of Health-funded liver transplantation study by Longworth and colleagues (reported in Wright and colleagues[78])

were not available from the sources used for unit costs, they were arbitrarily estimated as 10% of unit costs and used to model mean costs in the probabilistic sensitivity analysis using normal distributions.

Costs associated with disease states

Costs associated with disease states were taken from the HTA Mild HCV Trial (*Table 20*). For mild disease, resource use (work-up, treatment and monitoring) and cost data were collected alongside the RCT. To estimate the costs associated with moderate disease, cirrhosis, decompensated liver disease and HCC, an additional observational costing study was performed.[78] Costs include outpatient visits, inpatient days, investigations, procedures and drugs (in addition to combination therapy). It was assumed that severe disease incurs the same costs as moderate disease. Liver transplant costs were taken from a Department of Health study which measured individual patient resource use for patients undergoing liver transplant in the six UK liver transplant centres (n = 772).

Costs associated with combination therapy

Costs associated with combination therapy were taken from the HTA Mild HCV Trial (*Table 20*). Trial-based resource use was excluded. The treatment regimen used was standard IFNα and ribavirin.[78] Total treatment costs included the cost of IFN and ribavirin (where appropriate), outpatient visits, inpatient stays, investigations, procedures and other drugs. The average cost of each of these items was reported for mild and moderate disease and for patients with cirrhosis, decompensated liver disease and HCC. Total treatment cost for the model was calculated by adding these costs to the average cost of PegIFN, assuming that treatment duration with standard IFN and PegIFN are equal, and that resource consumption for all other types of health services when treated with PegIFN is equal to that when treated with standard IFN.

The cost of combination therapy with PegIFN and ribavirin was calculated using the average time of treatment for the two drugs, each multiplied by the corresponding average weekly unit cost. A 50:50 split was assumed in the use of the two preparations of PegIFN currently available in the UK. All costs were taken from the BFN.[99]

Average treatment duration was reported for mild patients by Wright and colleagues.[78] It was assumed that the duration of combination therapy does not depend on the stage of liver damage, that is, the duration of treatment is the same for mild to cirrhotic patients.

In the model, it was assumed that all patients would be treated as intensively as possible, therefore costs and effectiveness reflect this assumption. It is likely that these differences would

TABLE 21 *Costs and resource use associated with case-finding in prisons*

Stage of process	Resource use	Cost[98]
Provision of health promotion information on a group basis to all new prisoners including offer and scheduling of appointment for pre-test discussion	Prison officer (1 hour per 10 new patients)	£48 per inmate tested (scenario one) £71 per inmate tested (scenario two)
Pre-test discussion	Prison nurse (30 minutes per patient) Prison doctor (30 minutes per patient) Counsellor (30 minutes per patient) Prison chaplain (30 minutes per patient)	£37 per inmate tested
Individual relay of results and post-test counselling	Positive result: Prison nurse (25 minutes per patient) Prison doctor (25 minutes per patient) Counsellor (25 minutes per patient) Prison chaplain (25 minutes per patient)	£34 per inmate with a positive result
	Negative result: Prison nurse (5 minutes per patient) Prison doctor (5 minutes per patient) Counsellor (5 minutes per patient) Prison chaplain (5 minutes per patient)	£6 per inmate with a negative result
If positive, referral of patient to specialist clinic for further investigation	Prison doctor (5 minutes per patient)	Included in cost of relaying positive result

not have an impact on the cost-effectiveness ratio, since the relationship between clearance, length of treatment and adherence is thought to be linear in the case of antiviral therapy for HCV.

An additional assumption used in the model is that differences in the cost of treatment by genotype are driven by adherence. These two events are explicitly incorporated in the model. The original technology assessment report did not report the average length of treatment separately specified for adherent and non-adherent patients.[42] It is possible for this reason that treatment costs in the model may be slightly overestimated in relation to the benefits gained.

Measures of variation were available for each of the subgroups of the original costs and for the time of treatment. Variations in the cost of treatment with PegIFN are obtained indirectly using variations for each of the cost components as originally reported.

The cost of post-transplant cirrhosis was inflated by the cost of a further transplant, using the probability of reaching a transplant waiting list and of receiving a transplant taken from the section 'Liver transplantation' (p. 22), with associated costs.

Costs of case-finding strategies

In all scenarios, it was assumed that phlebotomy is performed in the community. However, obtaining blood from former and current IDUs may not be straightforward and referral to hospital phlebotomy services may be necessary. This would slightly increase the costs associated with case-finding; the likely size of this effect is not estimable from available sources.

Costs in the general case

In the general case, the cost of identifying patients for HCV testing was assumed to be equivalent to a 2-minute consultation with a generic healthcare provider.

Costs of case-finding in prisons

Table 21 shows assumptions regarding resource use in the prison scenarios. The cost of providing the health promotion lecture is calculated as £4.07 per attending inmate. This is based on a group of 10 inmates for each lecture and includes the following gross salary and employer costs, training, overheads and capital costs. The cost was calculated assuming 37.5 working hours per week for 42 weeks of the year and assumes 70% 'contact time'. At a volunteer rate of 8.5%, this cost becomes £48 per inmate tested. This cost also includes the costs involved in scheduling appointments. Discussion surrounding testing may

TABLE 22 *Costs and resource use associated with case-finding in general practice*

Stage of process	Resource use	Cost
Identification of all patients in the practice with a documented history of current or former injecting drug use and the application of a computer flag for all identified patients (scenario one)	Practice manager (3 days for identification of patients and 1 hour to annotate records)	£36 per patient tested
Drafting and preparation of letter to all identified patients (scenario one)	Cost of preparation of one letter (5 minutes of nurse time including all cost components for salary, training and capital), stamp (£0.30), paper, ink, consumables (£0.15)	£5.50 per patient tested
Initial discussion of hepatitis C testing with all attending patients within age range (scenario two)	Average cost of doctor or nurse (additional 2 minutes/patient per consultation)	£15.70 per patient tested
Pre-test discussion	Nurse practitioner	£11 per patient
Individual relay of results and post-test discussion with referral if positive	Positive test: Doctor (20 minutes per patient) Negative test: Cost of preparation of one letter	£28 per patient with a positive test result £2.70 per patient with negative test result

TABLE 23 *Costs and resource use associated with case-finding in drug and alcohol services*

Stage of process	Resource use	Cost
Pre-test discussion	Nurse practitioner	£11 per patient tested
Individual relay of results and post-test discussion with referral if positive	Positive test: Doctor (20 minutes per patient) Negative test: Cost of preparation of one letter	£28 per patient with a positive test result £2.70 per patient with a negative test result

be undertaken by the prison nurses, prison doctors, dedicated counsellors or the prison chaplain. A mean figure derived from these four professions was used to estimate the cost of providing pre- and post-test discussions. All unit cost estimates are taken from Unit Costs of Health and Social Care 2004 published by the PSSRU at the University of Kent.[98]

Costs of case-finding in general practice

Assumptions regarding the costs associated with case-finding in general practice are detailed in *Table 22*. The number of patients in a practice with a documented history of current injecting drug use was estimated using data from the Office of National Statistics. An average list size per practice of 5705 patients was assumed, of whom 0.8% (n = 46) will have a history of current or former injecting drug use. The cost of the ELISA test is detailed in the section 'Testing and diagnosis cost' (p. 31). A fairly generous use of resources was assumed for the identification and flagging of former IDUs. Search codes to identify patients with a history of former injecting drug use are not in widespread use and, although patients may be identified through searches on medication use and referral to drug services, more in-depth searches may be necessary to locate all potential patients.

Costs of case-finding in drug and alcohol services

Assumptions regarding costs and resource use in case-finding in drug and alcohol services are detailed in *Table 23*.

Utility values

Utility values were taken from the HTA Mild HCV Trial and cost-effectiveness model.[78] The health states to which utility values were applied are shown in *Table 24*. For patients with mild disease,

TABLE 24 *Utility values*

State	Utility (SE)				
	Non-symptomatic	Symptomatic	During treatment	Sustained response	Non-responder
Mild	0.79 (0.024)	0.75 (0.024)	0.65 (0.002)	0.82 (0.005)	0.76 (0.003)
Moderate	0.68 (0.03)	0.64 (0.030)	0.55 (0.003)	0.72 (0.007)	0.65 (0.0042)
Severe	0.60 (0.03)	0.56 (0.030)	0.50 (0.003)	0.66 (0.006)	0.61 (0.006)
Cirrhotic	0.55 (0.054)	0.51 (0.054)	0.46 (0.005)	0.61 (0.006)	0.55 (0.0038)
HCC	0.45 (0.056)	0.41 (0.056)			
Decompensated liver disease	0.45 (0.056)	0.45 (0.056)			
Waiting list for liver transplant	0.45 (0.056)				
Liver transplant	0.45 (0.056)				
Post-transplant, decompensated	0.45 (0.056)				
Post-transplant, healthy	0.67 (0.067)				

SE, standard error.

information on health-related QoL was collected alongside the RCT. An additional observational study was conducted to collect data for patients with moderate disease and cirrhosis. Data from a large UK liver transplantation study were used for patients with decompensated liver disease, HCC and the transplant-related states.[100] QoL assessments were obtained using the EQ-5D, for which UK community preference values are available. These utility values represent the best available data since they were obtained from UK patients with hepatitis C using a preference-based measure.

Analysis of uncertainty

One way sensitivity analyses

Several approaches have been used to explore the impact of uncertainty on model output.

The sensitivity of the results to variations in each parameter considered singularly (one-way sensitivity) was explored using high and low limits for each parameter in a range of two standard errors.

The use of scenarios for particular subgroups serves the purpose of finding potential variations in the cost-effectiveness of testing by groups of potential clients targeted.

A subgroup analysis was conducted by age, which indicates time since infection.

In some cases, scenario analyses were conducted to explore uncertainties around selected parameters that were thought to have a potentially important effect on results.

Probabilistic sensitivity analysis

In this approach, the model is run 1000 times. In each run, input values for each parameter are drawn at random from appropriate distributions. The resulting 1000 different incremental cost-effectiveness ratios (ICERs) are presented graphically in two forms: as simple plots on a plane and in cost-effectiveness acceptability curves (CEACs). CEACs link the results of the analysis to decision-makers' willingness to pay for an additional QALY. The distribution of the 1000 cost-effectiveness ratios is analysed to demonstrate the probability that case-finding is cost-effective at a range of values for willingness to pay. The actual willingness to pay for a QALY may vary between individuals, services and policy makers. NICE has stated that interventions which yield benefits at less than £20,000–£30,000 per QALY should be considered cost-effective, although other considerations are important in taking specific decisions.

The values for utilities, costs and transition probabilities and the characteristics of distributions used in the PSA are detailed in *Tables 25–29*.

Transition probabilities were sampled from beta distributions with characteristic parameters, α and β, derived from the mean and the standard error of the central estimates. Utilities were sampled from beta distributions with upper and lower bounds obtained from standard errors of the original data. Costs were sampled from the normal distribution since, although cost data are well known for being skewed to the left, the model uses estimates of their means, and these are normally distributed.

TABLE 25 *Probabilistic distributions used for population characteristics in the model*

	Distribution (mean, standard error)
Gender (males)	Uniform (0.68, 0.016)
Alcohol (males)	Uniform (0.40, 0.000)
Alcohol (females)	Uniform (0.20, 0.000)
ALT, mild	Uniform (0.57, 0.030)
ALT, moderate	Uniform (0.82, 0.034)
ALT, severe	Uniform (0.83, 0.042)
Relative risk, % alcohol risk drinkers	Uniform (0.65, 0.233)

TABLE 26 *Probabilistic distributions used for cost data in the model*

	Cost, distribution and parameters (mean, standard error [£])				
State	**Non-symptomatic**	**Symptomatic**	**Treatment cost**	**Sustained response**	**Non-responder**
Mild	Normal (138, 40)	Normal (138, 40)	Normal (mean 11,425)	Normal (259, 348)	Normal (118, 26)
Moderate	Normal (717, 76)	Normal (717, 76)	Normal (mean 11,529)	Normal (717, 76)	Normal (730, 64)
Severe	Normal (717, 76)	Normal (717, 76)	Normal (mean 11,529)	Normal (717, 76)	Normal (717, 76)
Cirrhotic	Normal (1,138, 224)	Normal (1,138, 224)	Normal (mean 11,938)	Normal (1,138, 224)	Normal (1,138, 224)
HCC	Normal (8,127, 1,910)	Normal (8,127, 1,910)			
Decompensated liver disease	Normal (9,120, 1,519)	Normal (9,120, 1,519)			
Waiting list for liver transplant	Normal (8,413, 930)				
Liver transplant	Normal (27,330, 2,885)				
Post-transplant, decompensated	Normal (9,538, 9,538)				
Post-transplant, healthy	Normal (1,385, 355)				

For all parameters, since standard errors were generally available for annual rates or longer, random values were sampled on the scale of the original values and then transformed into transition probabilities appropriate to the 3-month cycle length used in the model.

Value of information analysis

Value of information analysis is a method for establishing the societal value of acquiring additional information to inform a policy decision.[101] Decisions about how services should be organised in the future, based on current information, are always likely to contain some degree of uncertainty. The probabilistic framework for this analysis, described above, makes this explicit and reflects the impact of uncertainty across all parameters. The CEAC demonstrates, for a given willingness to pay for an additional QALY, the probability that case-finding would, in fact, be a cost-effective use of resources. The complement of this probability is therefore the chance that the decision to adopt would be 'wrong', with attendant costs in terms of health benefits and resources foregone. These costs, representing the consequences of a wrong

TABLE 27 *Probabilistic distributions used for utility data in the model*

State	Utility, distribution and parameters				
	Non-symptomatic	**Symptomatic**	**During treatment**	**Sustained response**	**Non-responder**
Mild	Beta (221, 59)	Beta (237, 79)	Beta (33,729, 18,162)	Beta (5,765, 1,265)	Beta (16,830, 5,315)
Moderate	Beta (167, 79)	Beta (167, 94)	Beta (14,851, 12,151)	Beta (3,252, 1,265)	Beta (8,231, 4,432)
Severe	Beta (163, 109)	Beta (156, 123)	Beta (13,637, 13,637)	Beta (4,386, 2,259)	Beta (4,282, 2,795)
Cirrhotic	Beta (47, 38)	Beta (44, 42)	Beta (3,953, 4,641)	Beta (4,297, 2,748)	Beta (9,270, 7,585)
HCC	Beta (35, 42)	Beta (31, 45)			
Decompensated liver disease	Beta (35, 42)	Beta (35, 42)			
Waiting list for liver transplant	Beta (35, 42)				
Liver transplant	Beta (35,42)				
Post-transplant, decompensated	Beta (35, 42)				
Post-transplant, healthy	Beta (32, 16)				

decision, are the 'cost of uncertainty' in the model. Correspondingly, the maximum value of reducing uncertainty in the decision problem, as modelled (i.e. the EVPI), is this cost of uncertainty.

The EVPI is calculated directly from the outputs of the probabilistic sensitivity analysis and yields a value across the cohort. In order to calculate the EVPI for the whole population, assumptions are necessary for (a) the size of the population for whom case-finding might be considered and (b) the expected lifetime of a case-finding programme.

In this case, it was assumed that the size of the population is 10,000 people. Somewhat arbitrarily, it was assumed that case-finding programmes for HCV might be expected to be in place for 15 years.

In addition to the population EVPI, which represents the upper limit for the value of further research into the cost-effectiveness of case-finding for HCV, partial EVPI is calculated from the model. This estimates the contribution to EVPI from individual (or sets of) parameters. This may help to direct the efforts of the research community, including sponsors of research, towards research programmes which will have the greatest benefit to future decision-makers. Partial EVPI analysis is computationally demanding. Therefore, in calculating partial EVPI, model inputs were grouped into the following categories:

- treatment and testing: prevalence of HCV; genotype mix; concordance with testing
- natural history: spontaneous presentation; progression to cirrhosis; risk of decompensation; effectiveness of combination therapy; transplant-related events (cirrhosis and decompensation); mortality
- costs: of testing, treatment and long-term consequences
- utilities.

In order to calculate partial EVPI values, it is necessary to aggregate across a double looping simulation structure. In this procedure, each sample value for the selected parameter of interest is simulated against all the sampled values for the remaining variables. Typically, this double looping process is computationally intensive and can entail main hundreds of thousands of simulation trials in order to yield a valid output.[102]

TABLE 28 *Probabilistic distributions for natural history data used in the model*

Transition probability natural history – rate per year	**Distribution: uniform (mean, standard error) or beta (α, β)**
Rate of spontaneous presentation, case-finding arm (mild to severe and HCC)	Uniform (0.075000, 0.0050000)
Rate of spontaneous presentation, spontaneous presentation arm (mild to severe and HCC)	Uniform (0.037500, 0.002500)
Cirrhosis to HCC, all arms	Beta (25.05, 977.07)
Cirrhosis to decompensate, all arms	Beta (40.01, 649.79)
Treated to sustained viral response (mild to severe, genotype 2 or 3)	Beta (1503.73, 78.80)
Treated to sustained viral response (cirrhosis, genotype 2 or 3)	Beta (6577.04, 7196.54)
Treated to sustained viral response (mild to severe, genotype 1 or 4)	Beta (57.37, 49.46)
Treated to sustained viral response (cirrhosis, genotype 1 or 4)	Beta (59.74, 190.46)
Treatment failure, mild to severe, genotype 2 or 3	Beta (57.03, 411.49)
Treatment failure, mild to severe, genotype 1 or 4	Beta (185.53, 215.21)
Treatment failure, cirrhosis	Beta (221.74, 202.65)
Decompensate to waiting list for transplant	Beta (29.59, 1449.95)
Waiting list transplant to liver transplant	Beta (61.52, 23.52)
Progression to decompensate after liver transplant	Beta (55.16, 2851.09)
Death from decompensate	Beta (72.85, 489.90)
Death from liver cancer	Beta (61.60, 6.84)
Post-transplant death	Beta (45.16, 255.88)

TABLE 29 *Probabilistic data for testing algorithm used in the model*

Transition probability testing algorithm – rate per year	**Distribution, beta (α, β)**
Prevalence – HCV antibodies	Beta (114, 118)
Prevalence – genotype 2 or 3	Beta (107, 99)
Spontaneous rate of clearance	Beta (183, 801)
Refuse ELISA	Beta (110, 105)
Refuse PCR	Beta (87, 55)
Proportion ineligible for treatment (absolute contraindications)	Beta (196, 1,349)
Refuse liver biopsy	Beta (149, 1,283)
Death from liver biopsy	Beta (225, 749,549)
Accept treatment, genotype 2 or 3	Beta (88, 58)
Accept treatment, after liver biopsy	Beta (101, 82)

Chapter 3
Results

The results of the evaluation are reported as follows. First, the general case is considered. In the section 'Costs and consequences of case-finding in the general case' (below) the costs and consequences of case-finding in a marginal analysis are reported. The incremental cost–utility of the general case analysis is presented in the section 'Cost–utility of case-finding' (p. 41) as a deterministic analysis, in which a single value is used for each input of the model. Results are presented overall and [in the section 'Results by age/duration of infection' (p. 43)] by subgroups according to age and sex. The section 'Analysis of uncertainty (general case)' (p. 49) reports the exploration of uncertainty in the general case, including one-way sensitivity analyses and PSA. We also explore the effect of changing the assumptions surrounding spontaneous presentation for testing in both arms of the model. The analysis of global EVPI (i.e. the total value of reducing decision uncertainty) is included alongside the probabilistic analysis in this section, but is discussed in more detail in the section 'Value of information analysis' (p. 55).

The cost–utility of case-finding in the three settings (prisons, general practice and drug and alcohol services) evaluated is presented in the section 'Cost–utility of case-finding in specific settings' (p. 55).

Costs and consequences of case-finding in the general case

Testing, diagnosis and initiation of treatment

The case-finding protocol modelled has a limited success in selecting individuals who complete the diagnostic process and are selected for treatment. Low rates of acceptance for both ELISA and PCR tests mean that a large number of individuals do not receive a diagnosis. These results are illustrated in *Figure 6*.

The model begins with a cohort of 1000 former IDUs amongst whom there is an underlying prevalence of HCV infection of 49% (41% have chronic HCV infection). The entire cohort is offered an ELISA test but only 49% accept this offer and 49% of these have a positive result (n = 240). Subsequently, 94 (39%) attend for further testing with PCR and specialist consultation. About 18% of these (n = 17) are assumed to have cleared the virus during the acute phase, leaving 77 with a positive PCR result. Of these, 10 are considered ineligible for treatment, 35 have genotype 2 or 3 and 32 have genotype 1 or 4. All individuals with genotype 2 or 3 are offered treatment and 21 accept it. Liver biopsy is offered to all patients with a genotype of 1 or 4, 88% (n = 28) accept this offer and 16 are offered treatment (12 patients with mild disease are monitored for progression). Twelve people refuse the offer of treatment or are lost to follow-up, leaving only four people who accept. Overall, 25 individuals are offered treatment, of whom 16 have mild disease, five have moderate disease, two have severe disease and two have cirrhosis.

Case-finding arm – longer term consequences

Over a 30-year period, in addition to those identified with a proactive case-finding approach, 284 individuals re-present and request HCV testing following an initial refusal; the breakdown by disease severity is shown in *Table 30*. A total of 219 individuals are treated (25 of whom were identified during the case-finding strategy). Treatment occurs in the majority of cases when liver damage is mild. About 93% (n = 204) of all treated cases achieve clearance of the virus. Fifteen individuals (7%) fail to clear the virus and proceed to later consequences.

Over 30 years, in the cohort of 1000 individuals, there are 5.1 cases of liver cancer and 9.8 cases of decompensated cirrhosis, 1.3 liver transplants are performed and 16.5 deaths due to HCV occur. Overall, there are 148 deaths.

Non-case-finding arm – longer term consequences

In the non-case-finding arm, 259 individuals present spontaneously for testing over a 30-year period, 192 have mild disease on presentation, 43 present with moderate disease, 16 have severe disease and seven are diagnosed with cirrhosis at presentation. A very small number of people (two per 10,000) present with HCC. A total of 176 individuals receive combination therapy, the

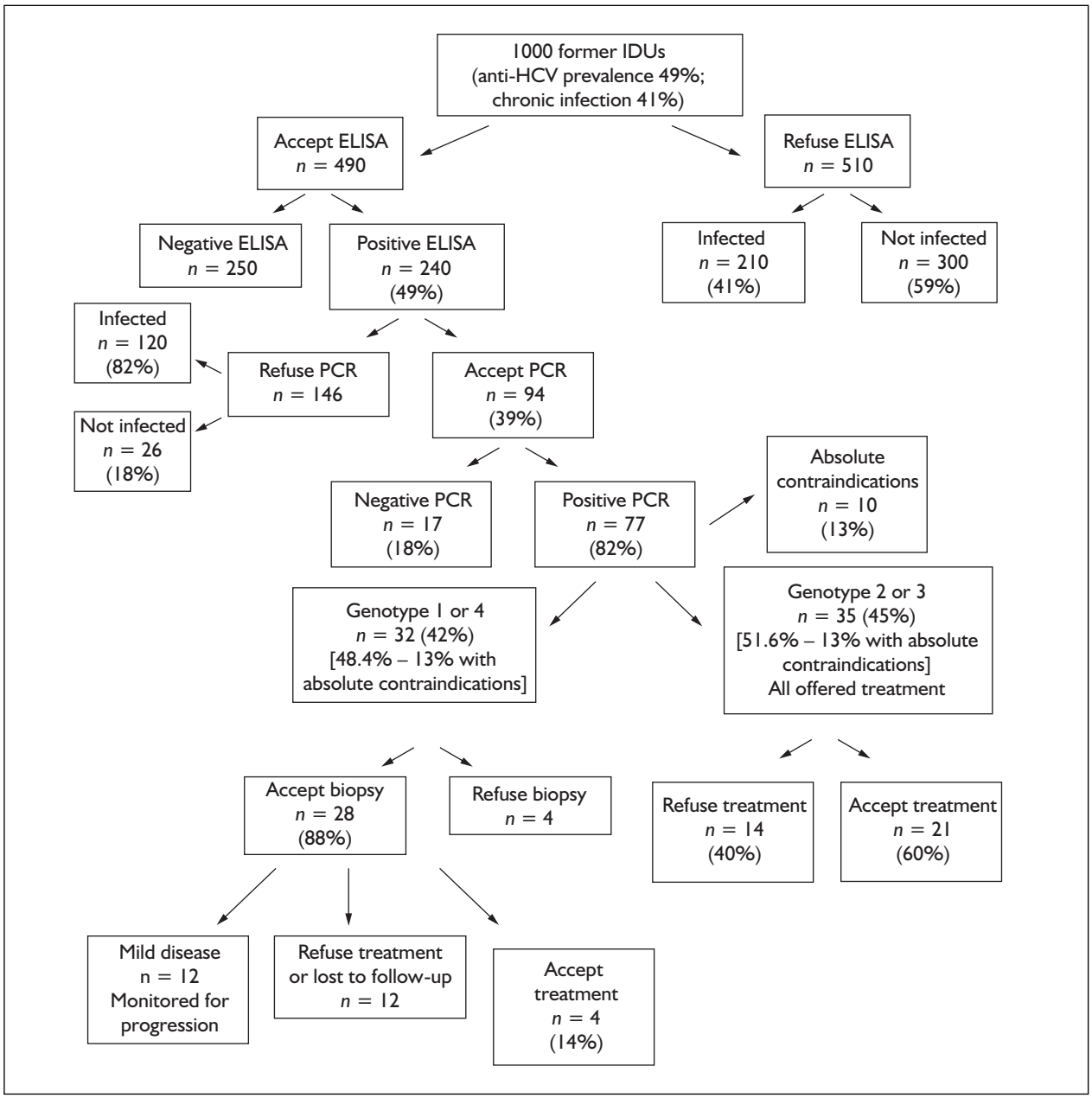


FIGURE 6 *Case-finding arm – testing, diagnosis and initiation of treatment*

majority of whom are infected with genotype 2 or 3 (n = 169; 96%). Rates of viral clearance are relatively high (n = 165; 94%).

Over 30 years, there are 6.7 cases of liver cancer and 13.3 cases of decompensated cirrhosis, 1.5 liver transplants are performed and 19.4 deaths due to HCV occur. Overall, there are 159 deaths in the cohort.

Effectiveness of case-finding – longer term consequences

Differences in longer term consequences are driven by the impact of differences in treatment rates in the two arms of the model.

Table 30 shows the number of events predicted by the model in the case-finding and non-case-finding cohorts (each containing 1000 individuals) over a 30-year period. Expressed for a larger population base of 10,000 people, case-finding for HCV would result in 16 fewer cases of liver cancer, 34.5 fewer cases of decompensated cirrhosis, 1.45 fewer liver transplants and 29.2 fewer deaths due to HCV. In addition, considering overall death rates, 118.1 deaths are averted for every 10,000 individuals tested.

Costs

Total discounted costs of care and treatment are given in *Tables 31* and *32*.

TABLE 30 *Descriptive results after 30 years: general case*

	Case-finding	Non-case-finding	Cases averted
Cases identified as a result of the case-finding strategy	**77**	**0**	
Disease severity at presentation			
Mild	57	0	
Moderate	11	0	
Severe	4	0	
Cirrhosis	5	0	
HCC	0.17	0	
Cases identified after spontaneous presentation/re-presentation	**284**	**259**	
Disease severity at presentation			
Mild	212	192	
Moderate	46	43	
Severe	17	16	
Cirrhosis	9	7	
HCC	0.28	0.22	
Cases treated as a result of case-finding	**25**	**0**	
Cases treated after spontaneous presentation/re-presentation	**194**	**176**	
Total number of cases treated:	219	176	
Genotype 2 or 3	207	169	
Genotype 1 or 4	11.9	7	
Cases achieving SVR	**204**	**165**	
Cases not achieving SVR	15	10	
Cases of decompensation	9.8	13.3	34.5/10,000
Cases of HCC	5.1	6.7	16/10,000
Cases on the transplant waiting list	1.5	1.7	
Liver transplants performed	1.3	1.5	14.5/100,000
Deaths due to HCV	16.5	19.4	29.2/10,000
Background deaths	131	140	
Deaths due to all causes	148	159	118.1/10,000

TABLE 31 *Total discounted costs of care, by main disease stages and arm of the model and the associated incremental costs: general case*

Disease stage	Case-finding (£)	Non-case-finding (£)	Incremental cost (£)
Testing	67,231	8,246	58,967
Mild	1,032,513	646,430	386,101
Moderate	501,237	311,781	189,270
Severe	187,924	114,558	73,383
Cirrhosis	170,729	79,426	91,321
HCC	5,879	3,486	2,410
Decompensated	348,810	386,638	–37,810
Liver transplant	37,844	41,820	–3,958
Total	2,352,167	1,592,385	759,684

The case-finding arm bears higher costs than its comparison owing to a higher expenditure on case-finding. However, the largest cost element associated with case-finding is the cost of treatment, with increasing additional costs by severity.

In the case-finding arm, the total cost of selecting individuals for treatment and of providing tested individuals with alcohol advice is £67,231, with a cost of £873 per positive individual diagnosed and £2689 per individual accepting treatment.

Cost–utility of case-finding

Results of cost–utility analysis and cost-effectiveness analysis are given in *Tables 33* and *34*, respectively.

In the general case, the model estimates an increase in total costs in the case-finding arm (*Table 34*). The additional cost of initial case-finding is not offset by lower costs of treatment or care for infected individuals over time. Case-

TABLE 32 *Total discounted costs of treatment, by main disease stages and arm of the model and the associated incremental costs*

Disease stage	Case-finding (£)	Non-case-finding (£)	Incremental cost (£)	Increase (%)
Mild	587,376	344,831	242,545	70.3
Moderate	160,999	86,920	74,079	85.2
Severe	61,223	32,122	29,101	90.6
Cirrhotic	71,981	28,960	43,021	148.6
Total	881,579	492,833	388,746	78.9

TABLE 33 *Cost–utility analysis: general case*

	Case-finding/1000		Non-case-finding/1000		Incremental/patient		
QALY	Costs (£)	Benefits	Costs (£)	Benefits	Costs (£)	Benefits	ICER (£/QALY)
Discounted	2,358,060	9,050	1,598,979	9,004	759	0.046	16,514
Undiscounted	6,242,849	12,357	5,095,115	12,286	1,148	0.071	16,190

TABLE 34 *Cost-effectiveness analysis: general case*

	Case-finding/1000		Non-case-finding/1000		Incremental/patient		
LYG	Costs (£)	Benefits	Costs (£)	Benefits	Costs (£)	Benefits	ICER (£/LYG)
Discounted	2,358,060	30,008	1,598,979	29,971	759	0.038	20,084
Undiscounted	6,242,849	41,016	5,095,115	40,958	1,148	0.058	19,786

finding is therefore not a cost-saving intervention. The incremental benefit of case-finding is small, corresponding to 0.046 QALYs. Therefore, the cost of one additional QALY is relatively small, £16,514. In terms of LYG, the cost of one additional LYG is £20,084.

These results are the combination of several factors. First, the additional number of individuals identified for treatment in the case-finding arm is small (a total of 25 individuals or 0.25% of the cohort). The number of individuals who receive HCV testing outside the efforts of a case-finding strategy is much larger than the number of individuals identified early for treatment because of case-finding. Second, non-tested, infected individuals in the case-finding arm progress towards later consequences relatively slowly. Liver damage remains mild for a considerable time and this is not associated with large decreases in QoL. Conversely, individuals who are treated as a result of case-finding experience a relatively large decrease in QoL (0.14 on the utility scale) early in the model. This decreases total QoL in the case-finding arm. This effect is combined with discounting, since early losses in QoL are relatively more important than losses in QoL in the longer term.

Impact of alcohol reduction on the cost–utility of case-finding

The inclusion of a brief intervention for the reduction of alcohol intake is important as a source of potential benefit for people who are identified through case-finding but are ineligible for treatment.

The maximum potential impact of alcohol reduction is shown by comparing a version of the model with a maximum prevalence of excessive alcohol intake (100%) to one with zero prevalence. The zero prevalence of excessive alcohol model results in additional benefits and lower costs because of the avoidance of long-term consequences of progression.

In the general case, 40% of males and 20% of females are assumed to have an excessive level of alcohol consumption. The impact of counselling to reduce alcohol consumption is shown in *Table 35*. This shows that, at this level of effectiveness and cost, the arm with counselling

TABLE 35 *Impact of alcohol reduction*

	Discounted costs (£)	Discounted benefits (QALYs)	Undiscounted costs (£)	Undiscounted benefits (QALYs)	Incremental costs (£) (discounted)	Incremental benefits (QALYs) discounted
Without alcohol counselling	2,359,155	9,048.36	6,250,500	12,354.57		
With alcohol counselling	2,358,079	9,049.59	6,242,939	12,356.60	–1,076	1.23

TABLE 36 *Cost–utility by duration of infection/age at testing (discounted)*

	Case-finding/1000		Non-case-finding/1000		Incremental/patient		
Duration of infection/age	Costs (£)	Benefits	Costs (£)	Benefits	Costs (£)	Benefits	ICER (£/QALY)
0–9 years 29 years old	1,730,671	10,835	1,123,209	10,809	607	0.026	23,036
20–29 years 43 years old	2,807,059	7,742	1,981,102	7,686	826	0.056	14,739
30+ years 50 years old	2,918,196	6,441	2,030,729	6,391	887	0.050	17,606

for excessive alcohol use dominates over the non-counselling arm, i.e. it costs less and results in more benefits.

The effect of counselling is relatively small given the small numbers of patients involved. The costs accrued in the non-counselling arm are higher than in the counselling arm because the costs incurred by people reaching long-term consequences as a result of excessive alcohol consumption are greater than the costs attributed to the counselling intervention. This cost saving would become zero only when the cost of alcohol counselling is assumed to be around £200 per patient.

Results by age/duration of infection

This section reports the cost–utility analysis carried out for three subgroups according to duration of infection, using age as an indicator [explained in the section 'Age and severity of liver disease' (p. 11)], based on the case mix from the Trent HCV Study Cohort Database (*Table 36*).

The subgroup for 10–19 years' duration since infection is not reported since the average age in this group is 35 years and so the results are very similar to those reported in the general case. Increasing duration of infection is associated with increased costs and benefits. The results indicate that case-finding in newly infected, younger individuals (duration of infection <10 years, mean age 29 years) is less likely to be cost-effective than the general case (£23,036 versus £16,514 per QALY, respectively). Case-finding in older individuals with a longer duration of infection is likely to be similarly cost-effective as the general case (£14,739 and £17,606 per QALY for 20–29 years and 30+ years, respectively).

Cost–utility and cost-effectiveness of case-finding in specific settings

Case-finding in prisons

Scenario one – general lecture

Results are given in *Tables 37–39*.

In this scenario, a general lecture on blood-borne viruses is delivered to all new prisoners during the induction programme. This is therefore a population-based approach; the volunteer rate for ELISA testing is 8.5% and it is assumed that 16% of those tested will have a positive ELISA result. The case-finding strategy results in the identification of 4.3 individuals and the subsequent treatment of 1.4. Rates of spontaneous and re-presentation are also low, reflecting the small pool of individuals within the cohort who have been exposed to the virus (n = 160).

Over the first 30-year period of the model, as a result of the case-finding strategy and later re-presentation for testing of those who initially refuse, 11.3 cases of decompensated cirrhosis, 5.2 cases of HCC and 9.5 deaths due to HCV are averted (in a cohort of 10,000).

TABLE 37 *Case-finding in prisons (scenario one) – descriptive results after 30 years*

	Case-finding	Non-case-finding	Cases averted
Cases identified as a result of the case-finding strategy	**4.3**	**0**	
Disease severity at presentation			
Mild	3.24	0	
Moderate	0.6	0	
Severe	0.23	0	
Cirrhosis	0.24	0	
HCC	0.01	0	
Cases identified after spontaneous presentation/re-presentation	**93**	**84**	
Disease severity at presentation			
Mild	69	63	
Moderate	15	14	
Severe	5	5	
Cirrhosis	3	2	
HCC	0.09	0.07	
Cases treated as a result of case-finding	**1.4**	**0**	
Cases treated after spontaneous presentation/re-presentation	**69.6**	**58**	
Total number of cases treated:	71	58	
Genotype 2 or 3	68	55	
Genotype 1 or 4	**3.9**	**2**	
Cases achieving SVR	**66**	**54**	
Cases not achieving SVR	5	3	
Cases of decompensation	3.2	4.3	11.3/10,000
Cases of HCC	1.7	2.2	5.2/10,000
Cases on the transplant waiting list	0.5	0.6	
Liver transplants performed	0.4	0.5	4.7/10,000
Deaths due to HCV	5.4	6.3	9.5/10,000
Background deaths	145	148	
Deaths due to all causes	151	155	38.6/10,000

TABLE 38 *Case-finding in prisons (scenario one) – cost–utility analysis*

	Case-finding/1000		Non-case-finding/1000		Incremental/patient		
LYG	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**ICER (£/QALY)**
Discounted	796,912	2,906	515,165	2,892	282	0.014	20,083
Undiscounted	2,129,945	3,969	1,639,954	3,947	490	0.022	22,153

TABLE 39 *Case-finding in prisons (scenario one) – cost-effectiveness analysis*

	Case-finding/1000		Non-case-finding/1000		Incremental/patient		
LYG	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**ICER (£/LYG)**
Discounted	796,912	30,258	515,165	30,250	282	0.008	33,770
Undiscounted	2,129,945	41,392	1,639,954	41,379	490	0.013	37,466

The costs associated with this strategy are relatively low compared with the general case, reflecting the low rates of diagnosis and treatment. However, the benefits obtained are also reduced and the resulting ICER is slightly higher (£20,083/QALY).

Scenario two – lecture with a focus on injecting drug use as a risk factor for HCV transmission
Result are given in *Tables 40–42*.

In this scenario, all new prisoners receive a lecture on blood-borne viruses within the induction

TABLE 40 *Case-finding in prisons (scenario two) – descriptive results after 30 years*

	Case-finding	Non-case-finding	Cases averted
Cases identified as a result of the case-finding strategy	**16**	**0**	
Disease severity at presentation			
Mild	12	0	
Moderate	2.18	0	
Severe	0.86	0	
Cirrhosis	0.91	0	
HCC	0.04	0	
Cases identified after spontaneous presentation/re-presentation	**191**	**226**	
Disease severity at presentation			
Mild	142	168	
Moderate	31	38	
Severe	11	14	
Cirrhosis	6	7	
HCC	0.19	0.19	
Cases treated as a result of case-finding	**5**	**0**	
Cases treated after spontaneous presentation/re-presentation	**168**	**154**	
Total number of cases treated	174	154	
Genotype 2 or 3	162	148	
Genotype 1 or 4	12.2	6	
Cases achieving SVR	**160**	**144**	
Cases not achieving SVR	14	9	
Cases of decompensation	7.1	11.6	44.8/10,000
Cases of HCC	3.7	5.8	21.9/10,000
Cases on the transplant waiting list	1.3	1.5	
Liver transplants performed	1.1	1.3	17.3/100,000
Deaths due to HCV	13.3	17.0	37.2/10,000
Background deaths	130	142	
Deaths due to all causes	143	159	157.4/10,000

TABLE 41 *Case-finding in prisons (scenario two) – cost–utility analysis*

	Case-finding/1000		Non-case-finding/1000		Incremental/patient		
QALY	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**ICER (£/QALY)**
Discounted	1,965,836	7,641	1,355,167	7,604	611	0.037	16,484
Undiscounted	5,451,764	10,434	4,313,040	10,376	1,139	0.058	19,535

TABLE 42 *Case-finding in prisons (scenario two) – cost-effectiveness analysis*

	Case-finding/1000		Non-case-finding/1000		Incremental/patient		
LYG	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**ICER (£/LYG)**
Discounted	1,965,836	30,057	1,355,167	30,034	611	0.023	26,773
Undiscounted	5,451,764	41,090	4,313,040	41,054	1,139	0.036	31,931

programme However, the lecture focuses on the risks of HCV transmission associated with injecting drug use. It was assumed that 12% of those attending the lecture will accept the offer of an ELISA test and that 42% of those tested will have a positive result.

As a result of initial case-finding efforts, 16 of the 420 individuals who have been exposed to the virus within the case-finding arm are identified and five receive antiviral therapy. After 30 years, a further 191 have re-presented later for testing; 226 individuals spontaneously present for testing

TABLE 43 *Case-finding in general practice (targeted approach) – descriptive results after 30 years*

	Case-finding	Non-case-finding	Cases averted
Cases identified as a result of the case-finding strategy	**77**	**0**	
Disease severity at presentation			
Mild	57	0	
Moderate	11	0	
Severe	4	0	
Cirrhosis	5	0	
HCC	0.17	0	
Cases identified after spontaneous presentation/re-presentation	**284**	**259**	
Disease severity at presentation			
Mild	212	192	
Moderate	46	43	
Severe	17	16	
Cirrhosis	9	7	
HCC	0.28	0.22	
Cases treated as a result of case-finding	**25**	**0**	
Cases treated after spontaneous presentation/re-presentation	**194**	**176**	
Total number of cases treated:	219	176	
Genotype 2 or 3	207	169	
Genotype 1 or 4	11.9	7	
Cases achieving SVR	**204**	**165**	
Cases not achieving SVR	15	10	
Cases of decompensation	9.8	13.3	34.5/10,000
Cases of HCC	5.1	6.7	16/10,000
Cases on the transplant waiting list	1.5	1.7	
Liver transplants performed	1.3	1.5	14.5/100,000
Deaths due to HCV	16.5	19.4	29.2/10,000
Background deaths	131	140	
Deaths due to all causes	148	159	118.1/10,000

TABLE 44 *Case-finding in general practice (targeted approach) – cost–utility analysis*

	Case-finding/1000		Non-case-finding/1000		Incremental/patient		
QALY	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**ICER (£/QALY)**
Discounted	2,357,013	9,050	1,598,869	9,004	758	0.046	16,493
Undiscounted	6,241,761	12,357	5,094,942	12,286	1,147	0.071	16,177

in the non-case-finding arm. A total of 174 individuals in the case-finding arm and 154 in the non-case-finding arm receive antiviral therapy.

The cost-effectiveness of this strategy is similar to the general case and remains in the region of £17,000 per QALY.

Case-finding in general practice

Targeted approach

Results of the targeted approach within general practice (*Tables 43–45*) are very similar to those obtained in the general case. The same data were used for the volunteer rate for ELISA testing (49%) and the proportion of tested individuals with a positive result, producing a strategy which is similarly effective in identifying individuals for treatment. There are slightly higher costs associated with this strategy owing to the need to identify patients with a history of injecting drug use from the practice records. However, the resulting ICER is virtually the same (£16,493 per QALY).

Case-finding in general practice (general population approach)

Results are given in *Tables 46–48*.

This is a population-based approach and is therefore similar to prison scenario one. However, in this situation, it is assumed that 10% of

TABLE 45 *Case-finding in general practice (targeted approach) – cost-effectiveness analysis*

	Case-finding/1000		Non-case-finding/1000		Incremental/patient		
LYG	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**ICER (£/LYG)**
Discounted	2,357,013	30,057	1,598,869	30,034	758	0.023	20,059
Undiscounted	6,241,761	41,090	5,094,942	41,054	1,147	0.036	19,771

TABLE 46 *Case-finding in general practice (general population approach) – descriptive results after 30 years*

	Case-finding	Non-case-finding	Cases averted
Cases identified as a result of the case-finding strategy	**4**	**0**	
Disease severity at presentation			
Mild	2.98	0	
Moderate	0.55	0	
Severe	0.21	0	
Cirrhosis	0.22	0	
HCC	0	0	
Cases identified after spontaneous presentation/re-presentation	**72**	**66**	
Disease severity at presentation			
Mild	54	49	
Moderate	12	11	
Severe	4	4	
Cirrhosis	2	2	
HCC	0.07	0.06	
Cases treated as a result of case-finding	**1.3**	**0**	
Cases treated after spontaneous presentation/re-presentation	**54.7**	**45**	
Total number of cases treated:	56	45	
Genotype 2 or 3	53	43	
Genotype 1 or 4	3	2	
Cases achieving SVR	**52**	**42**	
Cases not achieving SVR	4	3	
Cases of decompensation	2.5	3.4	8.8/10,000
Cases of HCC	1.3	1.7	4.1/10,000
Cases on the transplant waiting list	0.4	0.4	
Liver transplants performed	0.3	0.4	3.7/100,000
Deaths due to HCV	4.2	5.0	7.4/10,000
Background deaths	147	149	
Deaths due to all causes	151	154	30.1/10,000

TABLE 47 *Case-finding in general practice (general population approach) – cost–utility analysis*

	Case-finding/1000		Non-case-finding/1000		Incremental/patient		
QALY	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**ICER (£/QALY)**
Discounted	570,446	2,272	400,193	2,261	170	0.011	15,493
Undiscounted	1,607,480	3,103	1,276,695	3,085	331	0.017	19,109

individuals accept the offer of an ELISA test and 12% of those tested have a positive result. Overall, within the cohort there are 120 individuals who have been exposed to the virus. Hence the numbers of individuals identified and treated both as a result of the case-finding initiative and spontaneous and re-presentation are small. Four patients are identified as a result of case-finding and 1.3 of these receive antiviral therapy. A further 66 and 72 are tested as a result of spontaneous and

TABLE 48 *Case-finding in general practice (general population approach) – cost-effectiveness analysis*

	Case-finding/1000		Non-case-finding/1000		Incremental/patient		
LYG	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**Costs(£)**	**Benefits**	**ICER (£/LYG)**
Discounted	570,446	30,285	400,193	30,278	170	0.007	25,665
Undiscounted	1,607,480	41,433	1,276,695	41,422	331	0.010	31,847

TABLE 49 *Case-finding in drug and alcohol services – descriptive results after 30 years*

	Case-finding	Non-case-finding	Cases averted
Cases identified as a result of the case-finding strategy	**106**	**0**	
Disease severity at presentation			
Mild	79	0	
Moderate	14.5	0	
Severe	5.7	0	
Cirrhosis	6	0	
HCC	0.22	0	
Cases identified after spontaneous presentation/re-presentation	**394**	**360**	
Disease severity at presentation			
Mild	294	267	
Moderate	63	60	
Severe	23	22	
Cirrhosis	13	10	
HCC	0.39	0.31	
Cases treated as a result of case-finding	**34**	**0**	
Cases treated after spontaneous presentation/re-presentation	**270**	**245**	
Total number of cases treated:	304	245	
Genotype 2 or 3	288	235	
Genotype 1 or 4	16.5	10	
Cases achieving SVR	**283**	**229**	
Cases not achieving SVR	21	14	
Cases of decompensation	13.7	18.5	47.9/10,000
Cases of HCC	7.1	9.3	22.2/10,000
Cases on the transplant waiting list	2.1	2.4	
Liver transplants performed	1.9	2.1	20.2/100,000
Deaths due to HCV	22.9	27	40.6/10,000
Background deaths	123	135	
Deaths due to all causes	146	162	164/10,000

re-presentation in the non-case-finding and case-finding arms, respectively. Moderate numbers of instances of longer term consequences are averted.

The costs incurred are low in both arms, as are the benefits obtained, and the resulting ICER is £15,493 per QALY.

Case-finding in drug and alcohol services

Results are given in *Tables 49–51*.

The underlying prevalence of HCV infection is highest in this scenario (68%), reflecting the high numbers of current and former IDUs in contact with drug and alcohol services. It is assumed that 49% of individuals will accept the offer of a test.

The case-finding initiative therefore results in the identification of higher numbers of individuals; 107 of a possible 680 are identified during the initial effort; 34 of these receive antiviral therapy. Overall, 304 individuals are treated in the case-finding arm and 245 in the non-case-finding arm. In a cohort of 10,000, 47.9 cases of decompensated cirrhosis, 22.2 cases of HCC and 40.6 deaths due to HCV are averted.

The overall costs associated with this scenario are the highest (£2,443,336 in the case-finding arm) but the largest benefits are also seen (9119 QALYs in the case-finding arm). The incremental costs and benefits are £830 and 0.047 QALYs, respectively, producing an ICER of £17,515 per QALY.

TABLE 50 *Case-finding in drug and alcohol services – cost–utility analysis*

	Case-finding/1000		Non-case-finding/1000		Incremental/patient		
QALY	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**ICER (£/QALY)**
Discounted	2,443,336	9,119	1,613,513	9,071	830	0.047	17,515
Undiscounted	6,239,392	12,451	5,138,766	12,378	1,101	0.072	15,207

TABLE 51 *Case-finding in drug and alcohol services – cost-effectiveness analysis*

	Case-finding/1000		Non-case-finding/1000		Incremental/patient		
LYG	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**ICER (£/LYG)**
Discounted	2,443,336	30,011	1,613,513	29,968	830	0.044	19,059
Undiscounted	6,239,392	41,020	5,138,766	40,953	1,101	0.066	16,569

TABLE 52 *One-way sensitivity analysis – baseline population characteristics*

Parameter	**Range of variation**	**ICER – low (£/QALY)**	**ICER – high (£/QALY)**
Males in tested population (%) (general case = 68.3%)	50–80	16,333	16,624
Alcohol consumption in males (%) (general case = 40%)	20–50	16,802	16,368
Alcohol consumption in females (%) (general case = 20%)	10–30	16,581	16,446
% elevated ALT	50–90	16,679	16,309
% reduction in alcohol consumption from alcohol advice (base case = 35%)	0–50	16,756	16,418

Analysis of uncertainty (general case)

One-way sensitivity analysis

Tables 52–58 illustrate the impact of varying each of the inputs on the ICER. Input values are changed one at a time. In each table, the column headed 'ICER – low' indicates the cost-effectiveness when the parameter is set at the lower end of the range of values and 'ICER – high' indicates the cost-effectiveness when the input is set at the higher end.

Population characteristics

Demographic characteristics of the population such as the gender mix, the level of excessive alcohol consumption and the proportion of the population with elevated liver disease markers (*Table 52*) may be important since they are independent risk factors for progression. However, they have a limited impact on the ICER.

Prevalence of HCV antibodies in the population

The prevalence of HCV antibodies in the population has little effect on the cost-effectiveness of case-finding (*Table 53*). Decreasing the prevalence from 49% in the general case to 10% produces an ICER of £20,517, and the ICER remains below £17,000 when prevalence is set at 90%. A similar limited effect occurs with variations in the rate of spontaneous clearance of the virus and with variations in the proportion of individuals infected with genotype 2 or 3 versus genotype 1 or 4.

Rates of acceptance of testing and treatment

There is a small effect of the rates of refusal of ELISA and PCR tests on the cost-effectiveness of case-finding (*Table 54*). This result is counterintuitive, since the ICER increases as adherence increases. This is because, as rates of

TABLE 53 *One-way sensitivity analysis – prevalence of HCV antibodies*

Parameter	Range of variation	ICER – low (£/QALY)	ICER – high (£/QALY)
Prevalence of HCV antibodies (%) (general case = 49%)	10–90	20,517	16,351
Proportion of individuals with genotype 2 or 3 versus 1 or 4 (%) (general case = 52%)	40–60	18,890	15,550
Rate of spontaneous clearance (%) (general case = 18.6%)	10–30	16,452	16,620

TABLE 54 *One-way sensitivity analysis – rates of acceptance of testing and treatment*

Parameter	Range of variation	ICER – low (£/QALY)	ICER – high (£/QALY)
Rate of refusal of HCV antibodies test (%) (general case = 51%)	0–95	19,194	13,739
Specificity ELISA (%) (general case = 95%)	90–100	16,511	16,516
Rate of refusal of HCV PCR test (%) (general case = 61.1%)	0–95	20,044	14,169
Proportion of infected individuals with absolute contraindications (%) (general case = 13%)	5–20	11,632	26,949
Rate of refusal of liver biopsy (%) (general case = 10.4%)	0–95	16,386	17,803
Risk of death from liver biopsy (%) (general case = 0.03%)	0.01–1	16,495	17,462
Refusal of treatment, individuals with genotype 2 or 3 (%) (general case = 39.5%)	0–60	13,600	21,925
Refusal of treatment, individuals with genotype 1 or 4 (%) (general case = 45%)	0–60	15,592	16,888

adherence increase, the cost of testing and, more importantly, the number of individuals treated (with associated costs), increase and inflate the ICER. However, even with acceptance of 95%, the ICER stays well below £30,000.

The cost-effectiveness of testing is also sensitive to the proportion of individuals with genotype 2 or 3 who accept treatment. The ICER rises above £30,000 if the proportion of individuals who refuse treatment rises above 70%, from a baseline of 39.5%. For rates of acceptance of treatment in individuals with genotype 1 or 4, there are no large variations in the ICER over the range of plausible values. The effect on cost-effectiveness of assuming high adherence for blood and diagnostic tests and treatment is presented in the section 'High acceptance of testing and treatment' (p. 54).

Costs of the testing algorithm

The model is not sensitive to changes, within credible limits, in test performance of ELISA and PCR. Variations in the cost of testing were explored using a range of ±2 standard errors from the mean. The cost of blood and diagnostic tests and the cost of providing testing do not have a large impact on the ICER, which remains under £17,000/QALY (*Table 55*).

Effectiveness of combination therapy

The estimates for SVR according to severity of disease and genotype were scaled down by a common factor to investigate the impact of lower SVR rates being seen in practice than in the randomised controlled trials of combination therapy. *Figure 7* shows the impact on the ICER.

The ICER exceeds £30,000 per QALY only when the SVR rates are 0.575 of those modelled in the base case, that is, that SVR occurs in

- less than 54.6% of people with chronic hepatitis and genotypes 2 or 3
- less than 30.9% of people with chronic hepatitis and genotypes 1 or 4
- less than 27.5% of people with cirrhosis.

TABLE 55 *One-way sensitivity analysis – costs of testing algorithm*

Parameter	Range of variation	ICER – low (£/QALY)	ICER – high (£/QALY)
Cost of offering ELISA (£) (general case = £6.40)	3–30	16,437	17,043
Cost of ELISA test (£) (general case = £17)	3–30	16,360	16,657
Sensitivity ELISA (%) (general case = 97%)	90–100	16,403	16,569
Specificity ELISA (%) (general case = 95%)	90–100	16,511	16,516
Cost of offering PCR test (£) (general case = £30.70)	10–90	16,402	16,833
Cost of PCR test (£) (general case = £130)	50–200	16,346	16,661
Cost of genotyping (£) (general case = £94)	70–120	16,478	16,553
Cost of alcohol counselling-harm reduction (£) (general case = £22)	15–40	16,512	16,519
Cost of liver biopsy (£) (general case = £249)	150–300	16,450	16,546

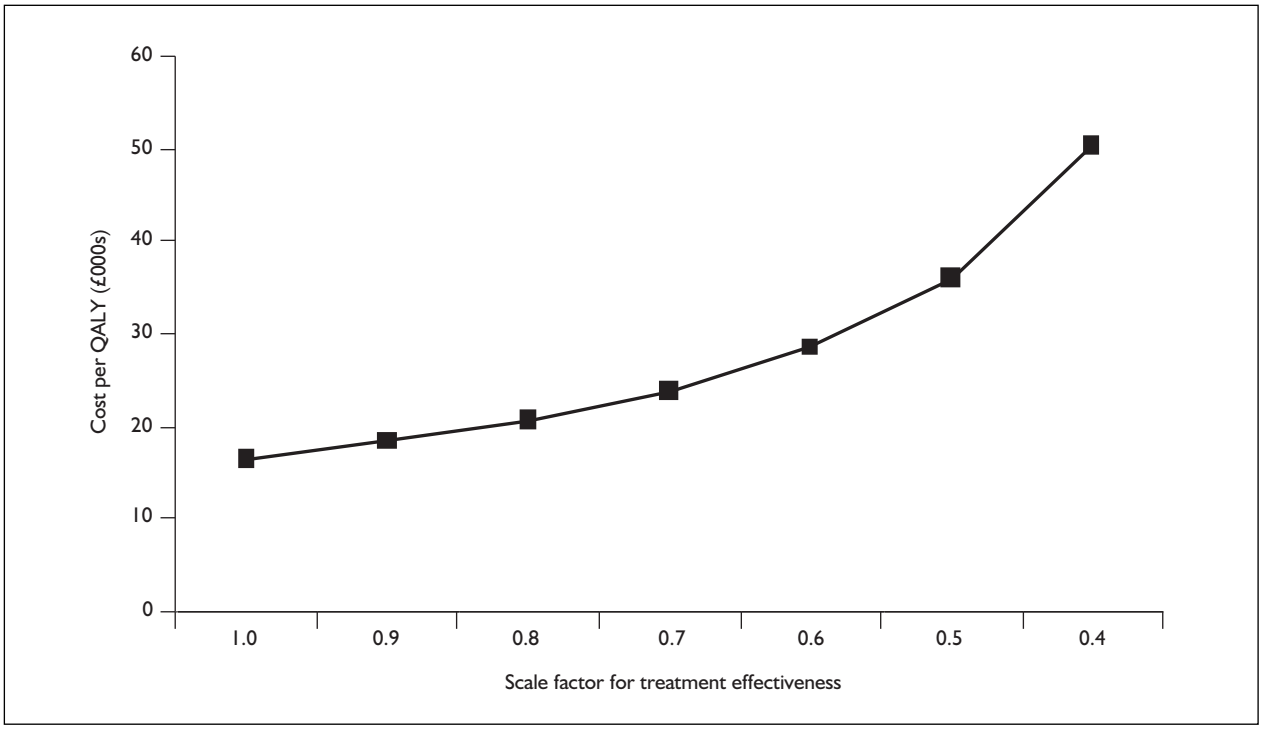


FIGURE 7 *Effect of reducing SVR on cost-effectiveness of case-finding*

Distribution of disease severity in the population
Variations in the distribution of disease severity at testing have a large impact on the cost-effectiveness of case-finding. If the rate of cirrhosis in the population increases to 20%, the ICER is reduced to £8491 per QALY, reflecting the increase in benefits associated with treating individuals with more severe disease (*Table 56*). Similarly, if the proportion of individuals with mild disease is increased to 95%, the ICER increases to £27,527 per QALY.

TABLE 56 *One-way sensitivity analysis – distribution of disease severity at testing*

Parameter	Range of variation	ICER – low (£/QALY)	ICER – high (£/QALY)
Rate of cirrhosis in population (%) (general case = 5.9%)	3–20	20,738	8,491
Rate of severe disease in population (%) (general case = 5.4%)	3–20	16,861	14,890
Rate of moderate disease in population (%) (general case = 13.7%)	5–30	14,926	19,618
Rate of mild disease in population (%) (general case = 74.8%)	50–95	12,523	27,527

TABLE 57 *One-way sensitivity analysis – longer term outcomes*

Parameter	Range of variation	ICER – low (£/QALY)	ICER – high (£/QALY)
Incidence of HCC (% per annum) (base case = 2%)	1–6	16,364	16,947
Incidence of decompensation (% per annum) (base case = 5.8%)	1–10	20,232	15,348
Waiting list for liver transplant (% per annum) (base case = 2%)	1–10	16,506	16,546
Mortality from decompensation (% per annum) (base case = 12.9%)	10–50	16,722	16,027
Mortality from liver cancer (% per annum) (base case = 90%)	70–99	16,581	16,476
Death after transplant (% per annum) (base case = 15%)	5–30	16,783	16,425

Longer term outcomes

With the exception of the incidence of decompensated liver disease, there is a limited impact of the incidence of longer-term outcomes on the ICER. The ICER remains below £17,000 as parameters for these events increase towards high rates within reasonable intervals (*Table 57*). If the incidence of decompensated liver disease is decreased to 1%, compared with 5.8% in the general case, the ICER increases from £16,514 to £20,232 per QALY.

Costs of longer term outcomes

Variations in the longer term costs for care for each of the states of chronic infection do not have a large impact on the ICER (*Table 58*). Changes in treatment costs also have little impact.

Effects of discounting

Changes in discount rates have a large impact on the results. *Table 59* displays three discount rates for costs and for benefits with the associated ICER values (£ per QALY). Results are shown for equal and differential discount rates. The general case is shown in bold (discount rate for costs and benefits 6 and 1.5%, respectively). It is interesting to note that using the currently recommended (HM Treasury) discount rate of 3.5% for both costs and benefits produces a result of £33,235 per QALY, indicating that case-finding would be less likely to be cost-effective at the £30,000 per QALY level under these conditions.

Exploration of assumptions around spontaneous rates of presentation

This section considers the impact of changing assumptions regarding the rates of spontaneous presentation for testing.

Short-term increase in re-presentation rate in the case-finding arm. In this scenario, it was assumed that for 2 years after the initial offer of testing, rates of re-presentation are doubled (7.7%) in people who initially refuse the offer of an ELISA test. After

TABLE 58 *One-way sensitivity analysis – cost of longer-term disease states*

Parameter	Range of variation (cost per year)	ICER – low (£/QALY)	ICER – high (£/QALY)
Cost of mild disease (£) (general case = £138)	50–200	16,086	16,815
Cost of moderate or severe disease (£) (general case = £717)	300–1,500	14,632	20,047
Cost of cirrhosis (£) (general case = £1,138)	500–2,000	15,925	17,309
Cost of decompensation (£) (general case = £9,120)	5,000–15,000	16,885	15,983
Cost of HCC (£) (general case = £8,127)	4,000–12,000	16,487	16,539
Cost of liver transplant (£) (general case = £27,330)	20,000–40,000	16,525	16,495
Treatment costs			
Mild disease	Halved–doubled	13,875	21,791
Moderate to severe disease	Halved–doubled	15,391	18,759
Cirrhosis	Halved–doubled	16,046	17,450

TABLE 59 *Sensitivity analysis for different discount rates*

		Costs – discount rate		
		–1.5%	**3.5%**	**6.0%**
Utility (QALY) – discount rate	1.5%	22,045	19,113	16,514
	3.5%	38,333	33,235	28,715
	6.0%	74,957	64,989	56,151

TABLE 60 *Short-term increase in re-presentation: cost–utility analysis*

	Case-finding/1000		Non-case-finding/1000		Incremental/patient		
QALY	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**ICER (£/QALY)**
Discounted	2,041,141	9,026	1,599,000	9,004	442	0.023	19,401
Undiscounted	5,429,997	12,319	5,095,216	12,286	335	0.033	10,098

this, the rate of re-presentation returns to the same as spontaneous presentation in the non-case-finding arm (3.8%). Results show that this has little impact on the ICER (*Table 60*).

Equal rates of spontaneous presentation and re-presentation. Varying the rates of spontaneous and re-presentation from 2.5 to 10% has a considerable impact on the numbers of individuals presenting for testing and the associated ICER values (*Table 61*). At a rate of 2.5% per year, a total of 244 individuals spontaneously present in the non-case-finding arm compared with 199 individuals re-presenting in the case-finding arm (over the course of the model). This increases to 371 and 302 in the respective arms when the rate is increased to 10% per year.

As the rate of spontaneous and re-presentation increases, the difference between the two arms of the model, in terms of both costs and benefits, decreases. This is a reflection of the number of individuals identified through case-finding being swamped by the number of people who spontaneously/re-present.

No spontaneous or re-presentation. When the rates of spontaneous and re-presentation are set to zero, the ICER increases to £19,024/QALY (*Table 62*).

Probabilistic sensitivity analysis

The probabilistic analysis demonstrates considerable uncertainty. *Figure 8* shows the distribution of the ICER for 1000 runs of the model. The ICER for case-finding is positive

TABLE 61 *Equal rates of spontaneous and re-presentation – cost–utility analysis*

	Case-finding/1000		Non-case-finding/1000		Incremental/patient		
	Costs (£)	Benefits	Costs (£)	Benefits	Costs (£)	Benefits	ICER (£/QALY)
2.5% per year	1,656,493	8,997	1,311,215	8,982	345	0.015	23,199
5% per year	2,077,840	9,028	1,829,350	9,020	249	0.008	32,505
7.5% per year	2,358,079	9,049	2,173,944	9,047	184	0.002	65,765
10% per year	2,555,637	9,065	2,416,857	9,065	139	– 0.00063	Case-finding dominated

TABLE 62 *No spontaneous or re-presentation – cost–utility analysis*

	Case-finding/1000		Non-case-finding/1000		Incremental/patient		
QALY	Costs (£)	Benefits	Costs (£)	Benefits	Costs (£)	Benefits	ICER (£/QALY)
Discounted	976,148	8,947	474,545	8,921	502	0.026	19,024
Undiscounted	2,092,769	12,189	1,270,102	12,148	823	0.041	19,994

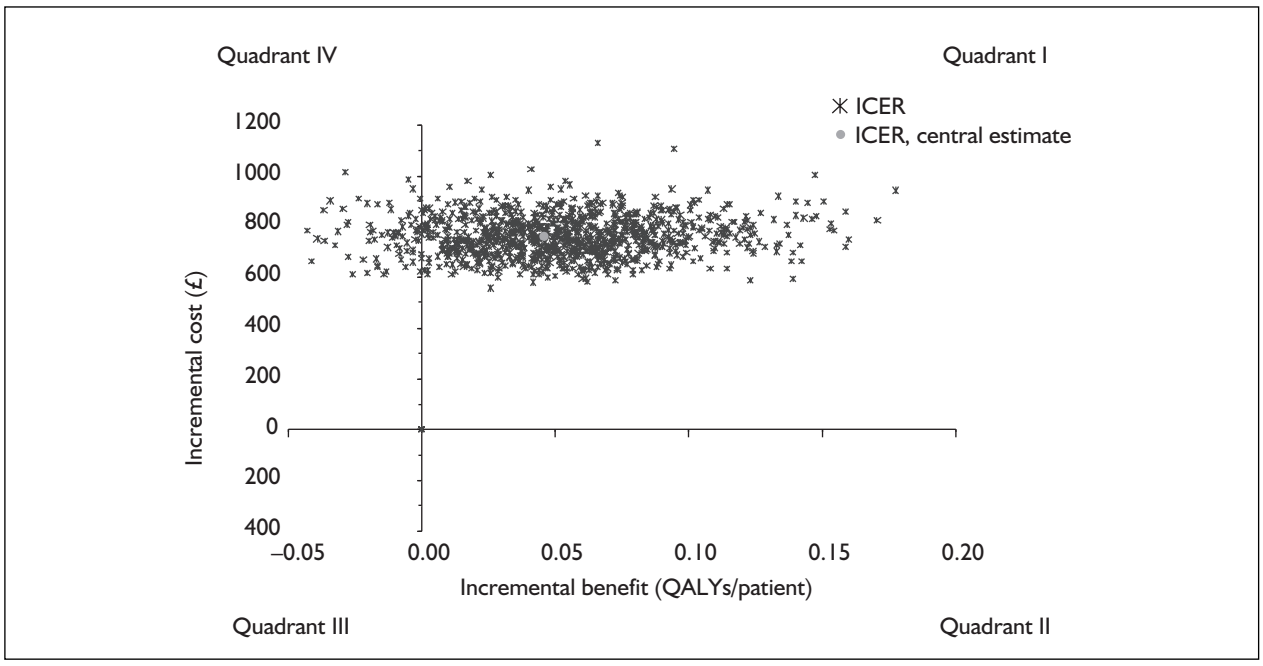


FIGURE 8 *General case: cost-effectiveness plane*

(quadrant I) in the majority of cases. In a limited number of cases, case-finding is 'dominated', that is, less effective and more costly than no case-finding (quadrant IV). Case-finding is very unlikely to be cost saving (quadrants II and III).

The CEAC is shown in *Figure 9*. If decision-makers are willing to spend more than £17,000 per QALY, then case-finding is likely to be considered cost-effective.

High acceptance of testing and treatment

Results are given in *Tables 63–65* and *Figures 10 and 11*. We considered high rates of acceptance of testing and treatment and calculated the ICER assuming that 95% of individuals offered ELISA and PCR accept the tests, that 95% of individuals accept an offer of biopsy and that 95% of individuals (in both genotype groups) accept the offer of treatment.

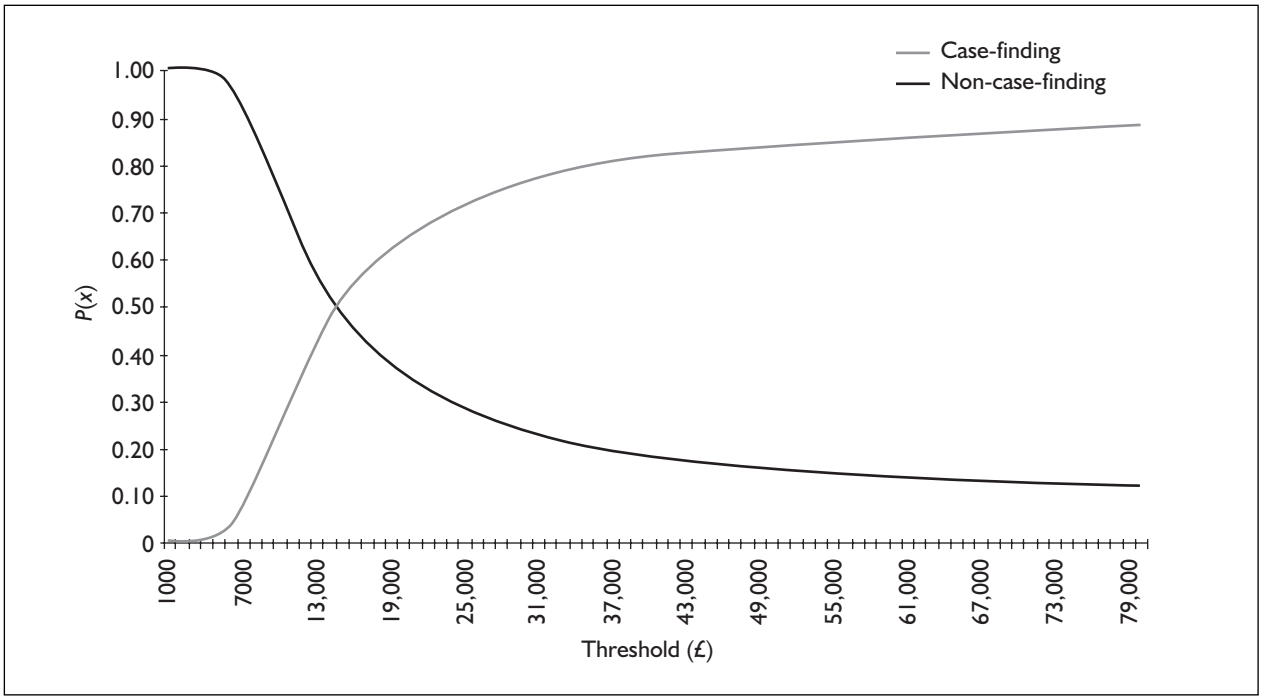


FIGURE 9 *General case – CEACs*

TABLE 63 *High acceptance of testing and treatment – cost–utility analysis*

	Case-finding/1000		Non-case-finding/1000		Incremental/patient		
QALY	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**ICER (£/QALY)**
Discounted	4,234,904	9,377	1,733,263	9,242	2,502	0.135	18,550
Undiscounted	7,788,271	12,814	5,420,501	12,618	2,368	0.196	12,058

TABLE 64 *High acceptance of testing and treatment – cost-effectiveness analysis*

	Case-finding		Non-case-finding		Incremental		
LYG	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**Costs (£)**	**Benefits**	**ICER (£/LYG)**
Discounted	4,234,904	30,136	1,733,263	29,967	2,502	0.168	14,852
Undiscounted	7,788,271	41,206	5,420,501	40,953	2,368	0.253	9,350

As in the general case, the model begins with a cohort of 1000 former IDUs amongst whom approximately 400 are chronically infected with HCV. Given such assumptions, only 40 of these remain undiagnosed following the offer of testing (ELISA and PCR). Of those who are tested (as a result of both the initial case-finding initiative and later re-presentation), 226 are treated, 190 of whom are infected with genotype 2 or 3.

Increased compliance has the effect of increasing both the cost of case-finding and, more substantially, the cost of treatment. As adherence with testing and treatment increases, the ICER becomes less favourable, although it remains below £20,000 per QALY.

Cost–utility of case-finding in specific settings

The probabilistic sensitivity analysis for case-finding in specific settings is explored in *Figures 12* and *13*.

Value of information analysis

The assumptions surrounding the value of information analysis are described in the section

TABLE 65 *High acceptance of testing and treatment – descriptive results after 30 years*

	Case-finding	Non-case-finding	Cases averted
Cases identified as a result of the case-finding strategy	**360**	**0**	
Disease severity at presentation			
Mild	270	0	
Moderate	49	0	
Severe	19	0	
Cirrhosis	20	0	
HCC	0.79	0	
Cases identified after spontaneous presentation/re-presentation	**48**	**264**	
Disease severity at presentation			
Mild	36	196	
Moderate	8	44	
Severe	3	16	
Cirrhosis	2	8	
HCC	0.04	0.19	
Cases treated as a result of case-finding	**189**	**0**	
Cases treated after spontaneous presentation/re-presentation	**37**	**204**	
Total number of cases treated:	226	204	
Genotype 2 or 3	190	194	
Genotype 1 or 4	35.4	10	
Cases achieving SVR	**196**	**191**	
Cases not achieving SVR	32	12	
Cases of decompensation	5.6	13.7	81.8/10,000
Cases of HCC	2.5	6.9	43.8/10,000
Cases on the transplant waiting list	1.0	1.7	
Liver transplants performed	0.9	1.5	62.9/100,000
Deaths due to HCV	9.9	19.7	98.1/10,000
Background deaths	124	142	
Deaths due to all causes	134	162	284.9/10,000

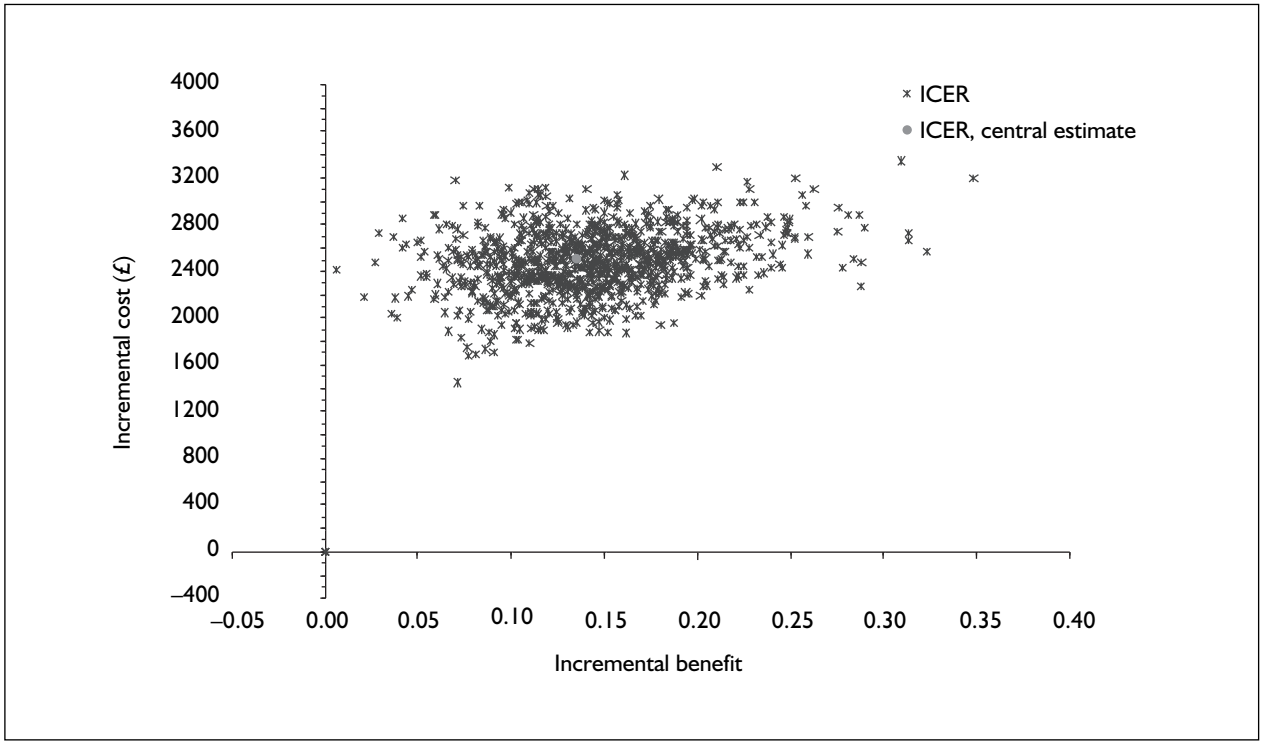


FIGURE 10 *High acceptance of testing and treatment – cost-effectiveness plane*

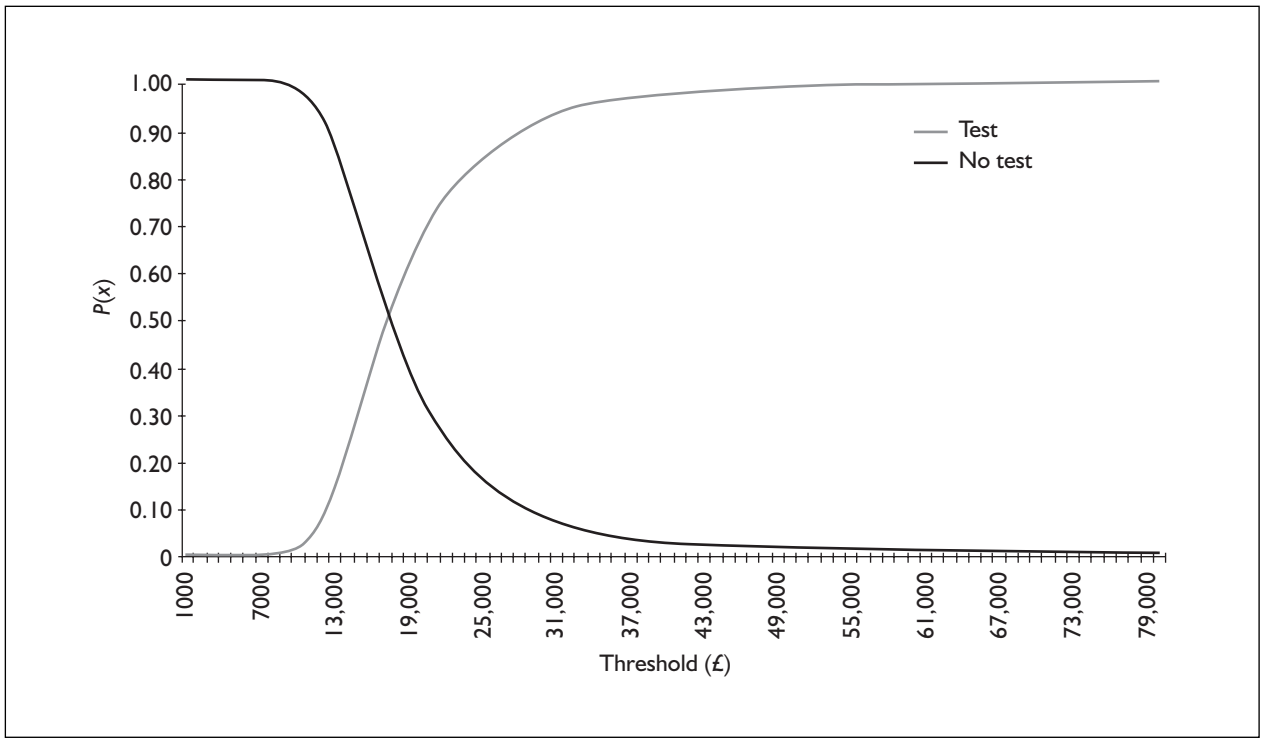


FIGURE 11 *High acceptance of testing and treatment – CEACs*

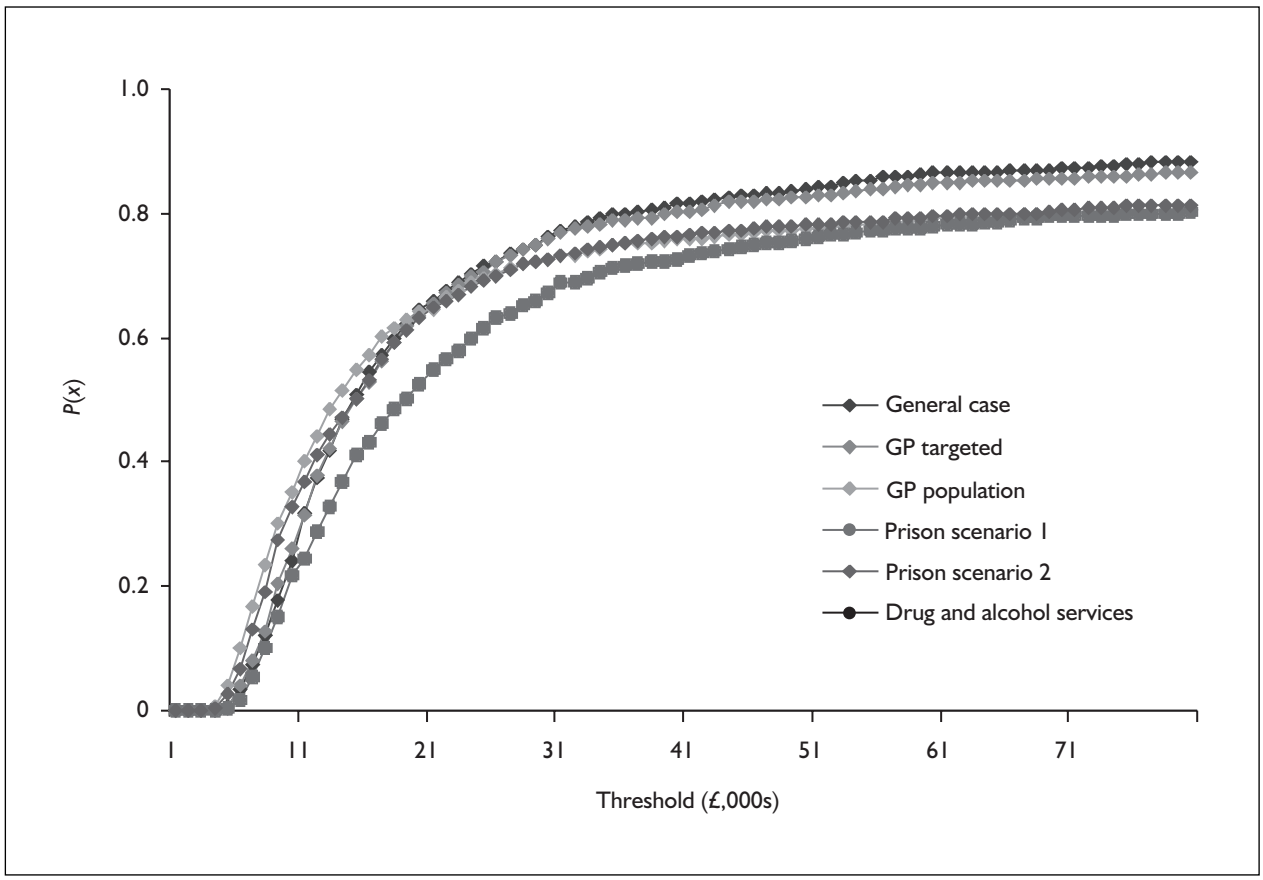


FIGURE 12 *CEACs for case-finding in specific settings compared with the general case*

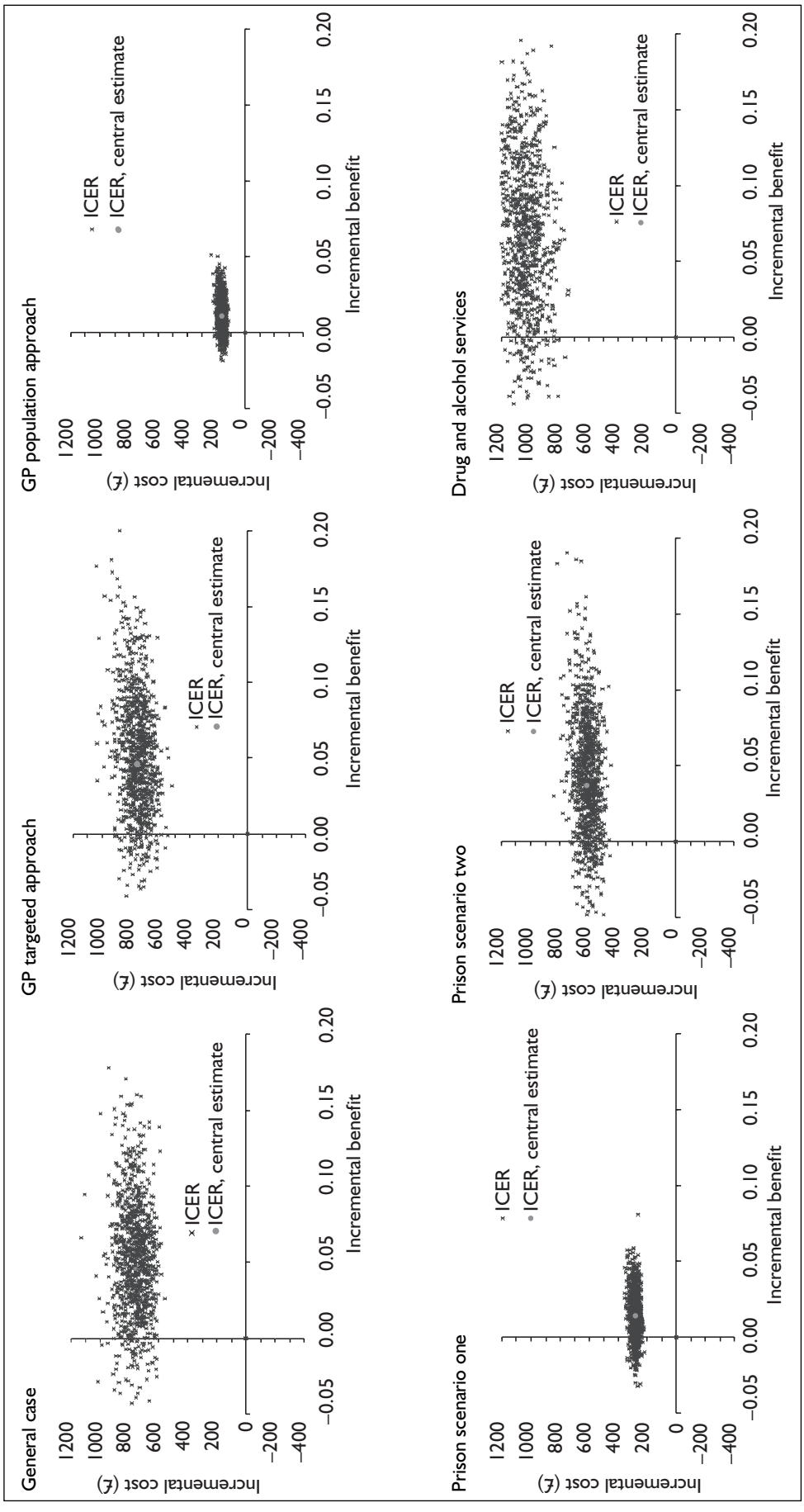


FIGURE 13 *Cost-effectiveness planes for case-finding in different settings compared with the general case*

'Values of information analysis' (p. 36). *Figure 14* shows the population EVPI for the general case. This is maximal at the point where the probability that case-finding is cost-effective is 50%, corresponding to the ICER value in the PSA. At this point, the population EVPI is estimated as £19.3 million. Given a willingness to pay for an additional QALY of £30,000, the population EVPI is £16.9 million.

Partial expected value of information (pEVPI) analysis was conducted for a range of specified parameters in the model and the results are given in *Table 66*. These show that the only parameters within the model with an associated value of information were the utilities. The utilities account for most of the overall value of information (the non-linearity of the model means that the sum of the partial value of information outputs would not normally be expected to equal the total EVPI).

These outputs should be treated with some caution since they are critically dependent on the assumed sampling distributions used in the Monte Carlo simulation. In many instances there is a lack of data relating to variance in the underlying variables of the model.

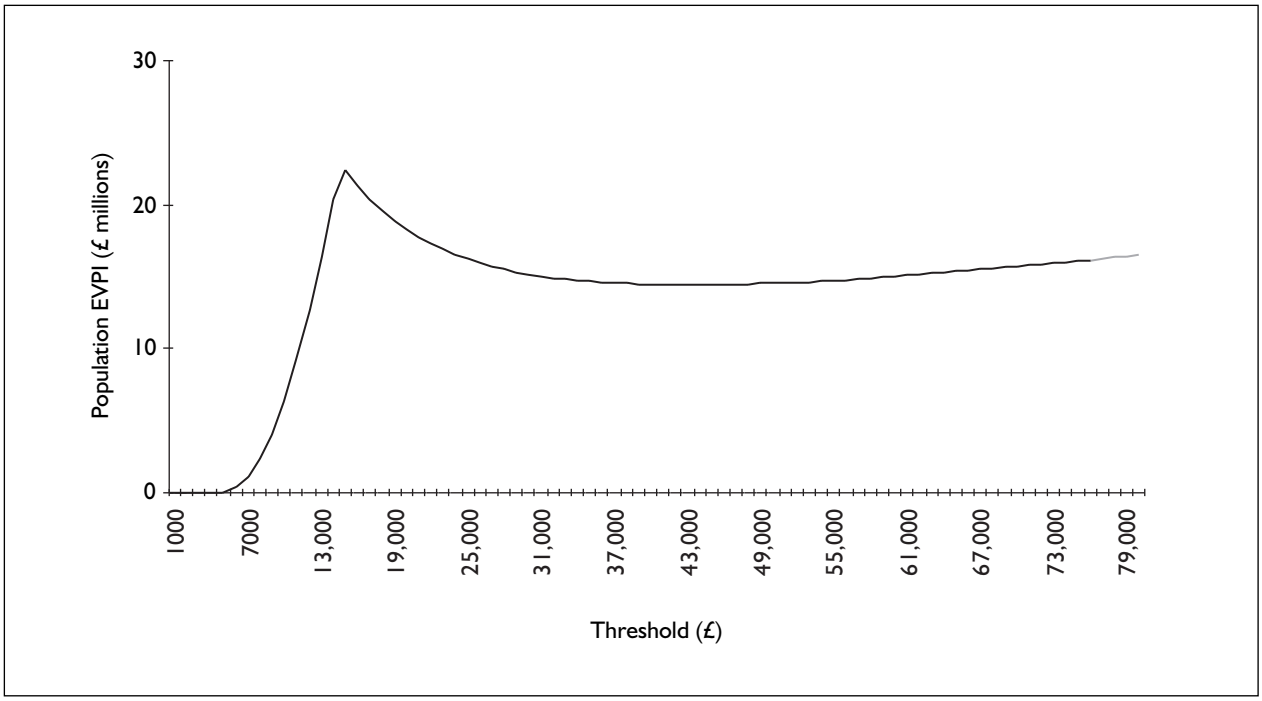


FIGURE 14 *Population EVPI*

TABLE 66 *Results from the pEVPI*

	Value of information population level (£ millions) at £30,000 willingness-to-pay per QALY threshold
Total EVPI	15.1
Prevalence of hepatitis C	0
Concordance with testing	0
Disease progression	0
Treatment effectiveness	0
Test costs	0
Treatment costs	0
Utilities	14.2

Chapter 4
Discussion

Summary and interpretation of main findings

Effectiveness of case-finding

Using this model, it has been demonstrated that case-finding strategies in the general case and in the exploratory analyses of potential case-finding settings are likely to be effective in terms of identifying and successfully treating additional individuals (*Table 67*). Moderate numbers of cases of advanced liver disease, hepatocellular carcinoma and deaths are prevented through the combination of systematic case-finding and re-presentation of individuals for testing following initial refusal (*Table 68*).

Cost-effectiveness of case-finding

Table 69 summarises the main results for the cost–utility analyses for the general case and the exploratory analyses in various case-finding settings. In all settings, case-finding is likely to cost more but to result in additional benefits, at a level which is likely to be considered cost-effective.

The analysis of the general case (in which a minimal amount of intervention was assumed at the point of offering testing) suggests a cost per QALY of around £17,000. Exploratory analyses suggest that the cost-effectiveness of case-finding is similar in the different settings and likely to be considered acceptable in all cases. It is important to note that the ICERs presented here are, in each case, comparisons with no case-finding. They do not indicate the incremental cost-effectiveness between the different approaches.

Subgroup analyses suggest that case-finding is likely to be more cost-effective in older people (i.e. those with longer duration of infection) than in those who were more recently infected (around £17,000 per QALY in those aged over 50 years compared with £23,000 per QALY in those aged 29 years).

Interpretation of the results

The one-way sensitivity analyses and pEVPI analysis confirm the importance of QoL as the

TABLE 67 *Summary of findings: additional individuals identified and treated as a result of case-finding (in a cohort of 1000)*

Approach	Additional individuals identified (*n*)	Additional individuals achieving SVR (*n*), at year 30
General case	77	39
Prisons – general lecture on blood-borne viruses	4.3	12
Prisons – focus on IDU	16	16
General practice – targeted approach	77	39
General practice – population approach	4	10
Drug and alcohol services	106	54

TABLE 68 *Summary of findings: longer term consequences averted as a result of case-finding*

Approach	No. of cases averted (per 10,000), at 30 years			
	Decompensated cirrhosis	HCC	Deaths due to HCV	Deaths due to all causes
General case	34.5	16	29.2	118.1
Prisons – general lecture on blood borne viruses	11.3	5.2	9.5	38.6
Prisons – focus on IDU	44.8	21.9	37.2	157.4
General practice – targeted approach	34.5	16	29.2	118.1
General practice – population approach	8.8	4.1	7.4	30.1
Drug and alcohol services	47.9	22.2	40.6	164

TABLE 69 *Summary of findings: cost–utility analysis (for a cohort of 1000 people)*

Approach	Cost (£)	QALYs	Incremental cost[a] (£)	Incremental QALYs[a]	ICER (£/QALY)[a]
Case-finding – general case	2,358,060	9050	759	0.046	16,514
Prisons – general lecture on blood-borne viruses	796,912	2906	282	0.014	20,083
Prisons – focus on IDU	1,965,836	7641	611	0.037	16,484
General practice – targeted approach	2,357,013	9050	758	0.046	16,493
General practice – general population approach	570,446	2272	170	0.011	15,493
Drug and alcohol services	2,443,336	9119	830	0.047	17,515

[a] Compared with no case-finding (note – estimates for costs and benefits in the non-case-finding arm vary considerably in the specific case-finding scenarios).

driver in this model. The following factors have important impacts on results:

- decrement in QoL at presentation
- decrement in QoL during treatment
- improvement in QoL following SVR in treated individuals
- improvement in QoL due to the avoidance of long-term consequences of HCV.

These effects are most marked in those with mild disease, because the majority of people who present with HCV have mild disease and individuals may be in this state for a long time during the model. Consequently, although the benefit of treatment, in terms of utility, is small (0.03), the cumulative disutility associated with this state throughout the course of the model and the corresponding impact of treatment are high. There is now good evidence for a decrement in utility associated with HCV infection using both preference (EQ5D) and non-preference (SF-36) based methods in patients and with societal values applied where appropriate[58,59]

The simulation is informed by utility data on the results of the HTA Mild HCV study, in which the presence of a utility decrement associated with mild disease was an important determinant of the cost-effectiveness of antiviral combination therapy in mild disease. Many people who present with mild disease may not develop clinically important sequelae during the rest of their lives and therefore treatment may be less cost-effective than in people with more severe disease, especially those diagnosed with more severe disease at a younger age.

Avoidance of the long-term consequences of HCV disease is, at the population level, a less important influence on the results as these events are affected considerably by discounting. However, the model demonstrates that this factor still makes a significant contribution to benefits from case-finding. *Figures 15* and *16* show the total cumulative, time-related incremental benefit between the model arms and partition this according to the component factors. Benefit differences between the arms were categorised according to the contributions made by identified states (e.g. treatment states, presentation states, disease states). The differences in state occupancy for these specific states and the associated utilities were then aggregated for different time horizons to create benefit differences for each of the identified categories.

The impact of reduced QoL **during** treatment is shown early in the model, and thereafter remains constant. 'Presentation decrement' refers to the small reduction in QoL that is assumed to be experienced by people who present spontaneously. This is shown as decreasing during the course of the model, as this factor reduces the difference between the arms of the model, since it affects only the non-case-finding arm. Around one-third of the cumulative difference in QALYs between case-finding and non-case-finding is a result of the avoidance of long-term complications of HCV infection.

Rates of spontaneous and re-presentation are important in the model. It has been shown that, given the assumptions modelled, the majority of people who will receive treatment for HCV will be identified outside arrangements for systematic case-finding. This is due, in part, to the relatively high rate of spontaneous presentation that is assumed (3.8% per annum). This was estimated from the only empirical data available and, as noted in earlier sections, is likely to be biased owing to the inclusion of people identified through existing case-finding initiatives. It is important to include this parameter in the model

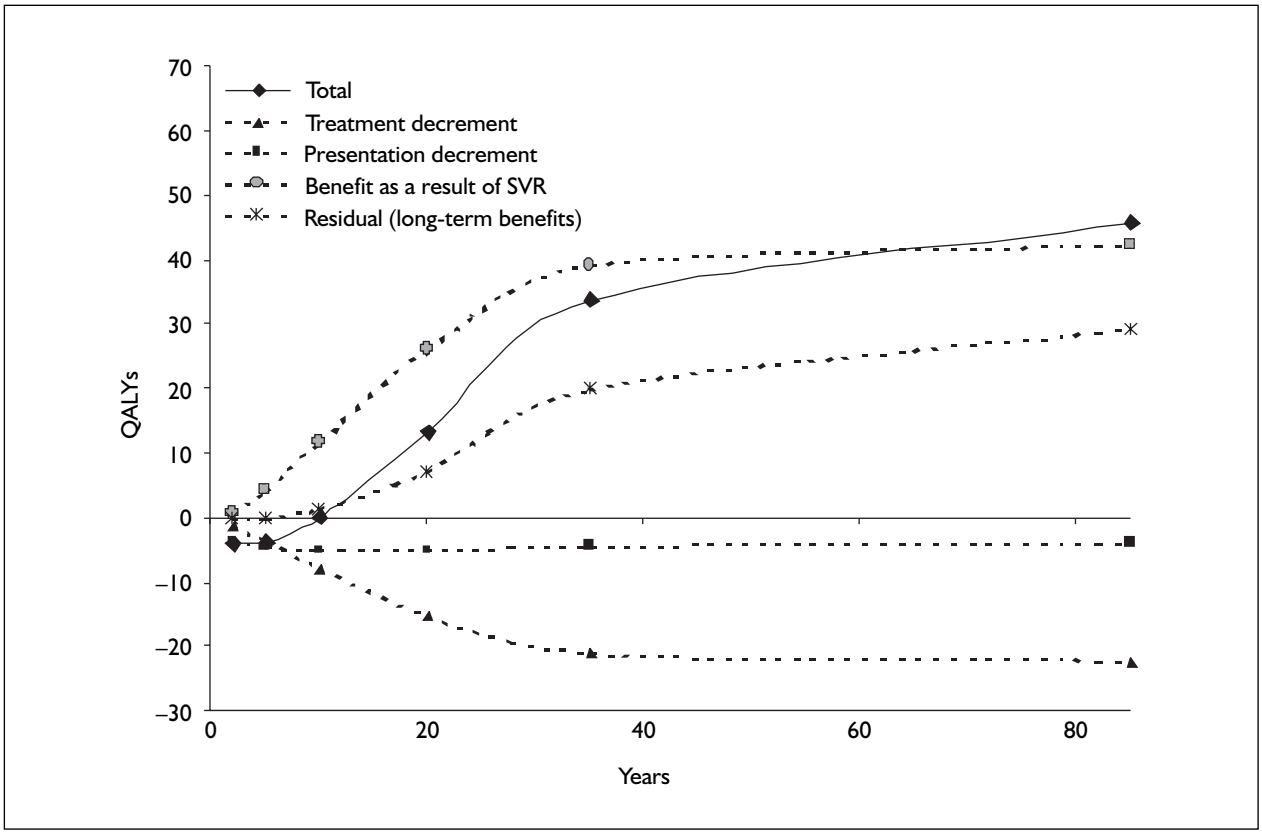


FIGURE 15 *Cumulative incremental QALYs between case-finding and non-case-finding showing the contribution of different components (SVR, sustained viral response)*

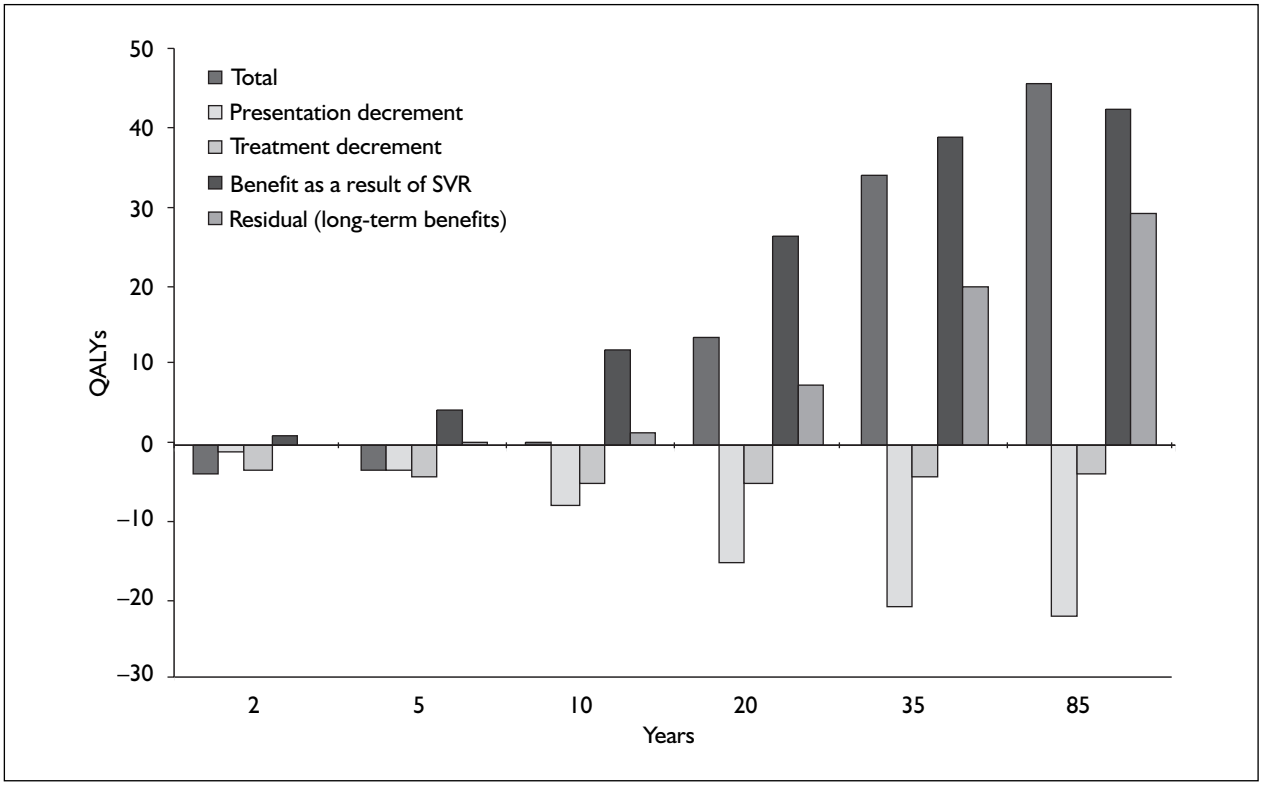


FIGURE 16 *Cumulative incremental QALYs between case-finding and non-case-finding at different time horizons (SVR, sustained viral response)*

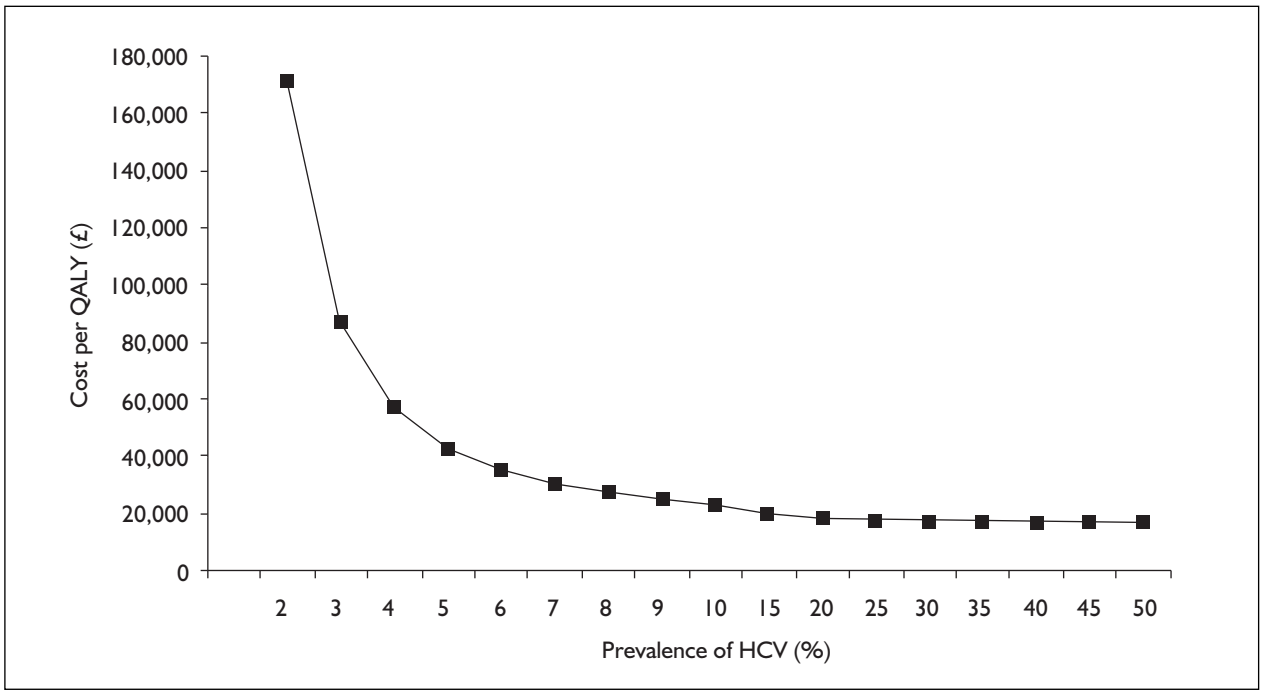


FIGURE 17 *Prevalence of HCV and cost-effectiveness of case-finding*

because, without such an estimate, the benefits of case-finding will be exaggerated. Once a value for spontaneous presentation is assumed, it is necessary to consider what would happen to people who are identified by case-finding but then lost to follow-up. Without allowing for some re-presentation, the impact of spontaneous presentation will gradually erode the benefits of case-finding and lead to a biased underestimate of the benefits of case-finding.

Discounting is important since the harms which are avoided by case-finding occur in the relatively distant future compared with the costs of case-finding and treatment which are incurred much earlier. Differential discount rates were used (1.5% for benefits and 6% for costs). However, if costs and benefits are discounted equally at 3.5%, the ICER rises above £30,000 per QALY.

The severity mix in the population of interest has an important effect because of the risk of progression. Where the proportion of people with cirrhosis is high, the risk of progression, on average in the cohort, is increased. Since a treatment benefit in cirrhosis is assumed, case-finding has the potential to interrupt progression. Although the number of people with cirrhosis is low, the much increased risk of progression makes this an important factor in the model. The size of the current epidemic of HCV is driven by two important factors: the prevalence of IDU and the prevalence of HCV among IDUs. The incidence and prevalence of HCV among IDUs is believed to be increasing, having fallen during the 1980s and 1990s, possibly owing to the impact of harm reduction efforts aimed at HIV.

It is notable that underlying prevalence, found to be important in the previous assessment of case-finding in GUM clinics and drug and alcohol services, seems to have little effect on the results in this analysis. In fact, there is an impact, but it does not have a significant effect on incremental cost-effectiveness until prevalence falls below 10% (*Figure 17*). This is broadly consistent with the previous findings in which prevalence in GUM clinics was assumed to be low. It may be surprising that the current assessment finds that a population-based approach in general practice (i.e. offering testing to the whole population) may be cost-effective. However, it is important to note that the estimates for the performance of this scenario come from a small empirical study in which the prevalence of HCV in people who accepted the offer of testing was much higher than would be expected from epidemiological studies. This strongly suggests that some selection (by patients or clinicians) is occurring between the offer of testing and its uptake. A similar finding was shown in a US study of screening for HCV based on a public awareness campaign and voluntary testing,[103] which identified a population with a relatively high prevalence of HCV.

Acceptance of testing and treatment were key parameters in the previous modelling study but appear less critical in this analysis. This is because in the current analysis a large proportion of people are tested outwith the initial case-finding programme and because the probabilities of acceptance are the same between model arms. There is no basis on which to model a difference in these parameters as there is a striking lack of suitable data, despite the increasing profile of HCV as a public health problem and the development of local, national and international guidelines for case-finding and treatment.

Strengths and weaknesses of the study

This is the first model of case-finding for HCV to consider the identification of potential individuals for testing in different settings. We considered a variety of screening approaches to reflect the most likely settings in which former IDUs may come into contact with healthcare workers. Strategies were included that might identify the stereotypical former IDU (e.g. in drug and alcohol services) and those who may have been recreational users many years earlier (e.g. the general population approach in general practice). Although, there are likely to be many more potential settings for case-finding, the stability of our results across different settings indicates that other targeted approaches to case-finding are likely to be considered cost-effective.

We also included a more extensive analysis of uncertainty than previous models including a probabilistic sensitivity analysis and the EVPI. These analyses show that, within levels of willingness to pay for additional health benefits that are accepted by some NHS decision-makers, case-finding for HCV is probably cost-effective. Nevertheless, considerable uncertainty remains, reflected in a high estimated population EVPI. Most of this uncertainty arises from the estimates of utility.

Treatment regimens for HCV have changed dramatically in the past decade. We modelled an approach that targets therapy according to likelihood of response and, therefore, achieves very high cure rates for infection. The analysis was based on available data and used a treatment duration of 48 weeks for all patients receiving combination therapy. Although this follows available trial evidence, it does not reflect current clinical guidance for shorter treatment durations and may lead to an overestimation of treatment costs in the model. However, several aspects of treatment that are not yet widely executed were also modelled. It should be noted that these assumptions will favour case-finding since (a) cost of treatment is reduced through avoidance of biopsy and (b) removing the requirement for biopsy may increase adherence to treatment. Conversely, by not including the stopping rules (e.g. ceasing treatment at 12 weeks if a reduction in viral load is not shown on quantitative PCR and treating patients with genotypes 2 or 3 for 24 weeks) in the treatment pathway, we slightly overestimated treatment costs, which will bias against case-finding.

Important population characteristics were included in the model of long-term disease progression, which allows exploration of the impact of factors such as alcohol reduction. Although the impact of other determinants of progression was not extensively explored, the sophistication required to achieve this, subject to the availability of appropriate data from the potential target population for case-finding, is present.

We modelled the potential cost-effectiveness of case-finding according to presumed severity and found that efforts to identify cases are likely to be most cost-effective where those cases are already more advanced.

There are some limitations to this assessment, which can be divided into the following broad areas

Injecting behaviour

We have not modelled treatment of people who are currently injecting drugs. However, in some settings, notably prisons, it is likely that a proportion of people who may be tested will be current injectors, and this may account for the variable, but generally low rates of treatment in the current limited available literature. This was not taken into account in the analysis. Current injectors are considered ineligible for treatment and therefore, apart from advice to reduce alcohol (which may be redundant in the prison setting), this group is excluded from treatment. It is possible that knowledge of HCV status would have an impact on harm reduction in use of injecting equipment, although our previous assessment demonstrated a lack of evidence, at that time, to support this.

The line between injectors and non-injectors may not be clear cut: people may relapse back into injecting. This may be important since, we speculate, a return to injecting is possible and likely to be dependent on the time since injecting ceased. Some people identified through case-finding as former injectors may therefore return to injecting. If they become re-infected with HCV, which is likely if they share injecting paraphernalia, the benefits of case-finding and treatment will be eroded. Such movement between states is not uncommon in practice: the population of former IDUs may include people maintained on methadone, those successfully detoxed with treatment, those previously dependent but ceased without treatment and recreational or opportunistic injectors. The actual mix of these groups in any setting is likely to vary, but is not currently known. By not accounting for the possibility of relapse in injecting, the model is therefore biased in favour of case-finding, although the size of the effect is not estimable.

Eligibility and acceptance

There is a striking lack of evidence on pathways to treatment, and this limited our ability to model the cost-effectiveness of case-finding in different settings and to reflect the possible differences between population subgroups. For example, alcohol use may interact with adherence and eligibility: people with significant alcohol use are unlikely to be considered eligible for treatment but may become so if intake is reduced. Time since injecting ceased may also be associated with adherence if, as time since injecting increases, former IDUs develop a more stable lifestyle, although this may not hold for people who remain users of drugs by other routes. Indeed, some high rates of adherence have been reported (e.g. to liver biopsy in the Trent Region). Essentially, there are currently insufficient data to explore this important aspect of case-finding in detail.

It was assumed that testing is completed within one cycle of the model, that is, 3 months. This may not reflect clinical reality, but this factor is unlikely to be important over the duration of the model.

The previous study showed, paradoxically given the prevalence of risk factors for infection, that drug and alcohol services are less likely to undertake case-finding than GUM clinics. One of the reasons for this may be lack of access to facilities for venepuncture in community drug treatment settings. This may account for limited acceptance of testing and may indicate scope for improvement. Research is under way to investigate the potential for salivary testing to increase uptake and the WASH studies[104] have already shown a greater acceptance rate of saliva testing over ELISA and studies of testing based on dried blood spots are under way (Hickman M, Imperial College, London: personal communication, 2005). Acceptance in the testing sequence is not shown to be particularly important in this model, which is in contrast to our previous assessment. This is due to the incremental nature of the current analysis and the fact that people who are not tested during initial case-finding are likely to be tested at some future date.

Effectiveness of combination therapy

We modelled a high rate of viral clearance and assumed that this results in avoidance of long-term benefits and an increase in utility. Although there is good evidence for a reduction in QoL in HCV infection, the uncertainty analysis demonstrates the critical importance of the size of this difference and the assumption that, in the very long-term, viral clearance will result in avoidance of long-term consequences.

The SVR rates shown in trials may not be demonstrated in practice. It has been shown that, if SVR rates are less than two-thirds of those shown in trials, then the cost-effectiveness of case-finding will exceed £30,000 per QALY. Data from one hepatology unit (Mutimer D, University of Birmingham: personal communication, 2005) shows that, in practice, intention-to-treat SVR rates for genotypes 1, 2 and 3 may be as low as these values. This may be due to poorer completion of treatment in practice than in clinical trials and further information on the effectiveness of treatment in routine practice is needed.

Our assumption that treatment prevents progression of cirrhosis is supported by less robust evidence than the evidence for the effectiveness of treatment in non-cirrhotic hepatitis.

Spontaneous and re-presentation rates

As detailed in Chapter 2, it is very difficult to model these factors accurately, although it is clear that they should be included in the model.

Our assessment of spontaneous presentation was based on an estimate of presentation rates for people with undiagnosed infection. This almost certainly overestimates spontaneous presentation,

although the size of the bias and its impact on the model estimates are not clear. The resulting estimate for rates of spontaneous presentation is high – we estimate that 3.8% of the currently infected population will come forward each year for testing.

Different rates for spontaneous presentation and re-presentation were modelled. Specifically, it was assumed that once people have been offered (but do not receive) testing there is a residual effect on re-presentation, that is that the re-presentation rate is higher than the spontaneous presentation rate. In the general case, re-presentation rates were assumed to be twice the spontaneous presentation rate throughout the course of the model. However, a more conservative assumption, that the re-presentation rate becomes the same as the spontaneous presentation rate after 2 years, did not materially affect the overall results.

Size of the infected population

The number of people whose infection status is currently unknown is not important for the general case analysis, since only people whose status is unknown are considered for the offer of testing. However, the size of this population, which is uncertain, is relevant in three ways:

- In some case-finding scenarios, where there is a cost associated with establishing whether people know their infection status. This does not apply to the prison- and GP-targeted scenarios. In the other scenarios, some resource may be used in establishing, as part of case-finding, that people already know their status but the time taken to do this is minimal and so the effect on the model is very likely to be unimportant.
- The overall cost of case-finding will depend on the size of the population of interest.
- The EVPI is driven by the size of the population for whom case-finding would be appropriate.

Case-finding scenarios

We have considered several simple scenarios which give broad outline of possible case-finding approaches but the design of case-finding programmes, in practice, would need to be tailored to individual settings and there are potentially a large number of possible approaches. Other potential settings in which testing might be offered include pharmacies (in needle exchange and supervised ingestion schemes) and NHS walk-in centres. Very little detailed information on case-finding approaches is available, despite programmes being carried out in the UK (as demonstrated in our previous survey and two reports of case-finding in prisons). Nevertheless, the results suggest that estimates of cost-effectiveness are fairly robust to changes in setting and approach.

Case-finding in general practice may be particularly important as a means of finding people who would not otherwise be identified as being at risk, such as people who had a short injecting career many years ago. However, there are many unanswered questions regarding the practical implications of case-finding in general practice. For example, the new GP contract supports increasing computerisation of notes. This, and the eventual implementation of the electronic patient record, may make searching based on computer records more feasible. However, it is likely that some practices will lag behind in this, and it is possible that these will be serving populations with a higher prevalence of former IDUs. Furthermore, approaches to searching for a history of IDU based on Read Codes in general practice systems need to be developed and tested.

It was assumed that treatment eligibility is the same in all case-finding scenarios. However, it seems reasonable to speculate that fewer people identified through drug services would be eligible than, for example, those identified through case-finding in general practice, because of a higher prevalence of homelessness, less support and a greater prevalence of psychological problems. Where possible, data specific to the settings modelled were used. However, such data are sparse and, in some cases, may be contradictory.

The prison population, in particular, may be prone to organisational factors which could influence treatment success. Movement of prisoners between establishments is very common and people may not be in one location long enough to initiate or complete treatment. Closer links between the Prison Medical Service and the NHS may improve coordination and mitigate against this. However, the prison population also has a higher prevalence of psychological problems, and prisoners face the challenge of obtaining adequate support and housing on release to guarantee continuity of treatment following rehabilitation into the community.

Further empirical research into case-finding in different settings will be necessary to resolve such uncertainties.

Case mix and disease progression

Data from the Trent cohort were relied on to estimate severity at presentation. This is among the most comprehensive data sources in England, although other approaches are possible. In particular, the projection model developed by Hutchinson and colleagues based on data from Glasgow is an alternative. It is likely that this would have estimated a more severe case mix at presentation, although whether this would be more representative of the UK in general is uncertain. A more severe case mix would, as shown in the subgroup analysis by duration of infection, tend to make the cost-effectiveness of case-finding more favourable. On the other hand, the use of the Trent database to inform the no case-finding arm of the model may increase the external validity of the analysis. Since current practice includes some case-finding, the analysis explores the potential cost-effectiveness of increasing case-finding from the current position.

If the scale of case-finding programmes increases, it is likely that individuals currently tested may not be representative of the total population of infected individuals. However, it is difficult to establish whether additional identified infected individuals will skew the potential tested population towards a less or more severe case mix at presentation.

A relatively simple model of progression of HCV was used, although one that is supported by the most comprehensive meta-analysis of epidemiological data. Nevertheless, it is possible that some assumptions regarding progression may not be correct, for example, that progression through mild, moderate and severe hepatitis is sequential and independent of age, that regression between hepatitis states does not occur and that progression to HCC can only occur after cirrhosis has developed. Although these factors are of considerable epidemiological and virological interest, it has been shown that the model of case-finding is relatively insensitive to assumptions regarding progression.

The representation of end-stage liver disease was simplified in the model. The reasons for this are explained in Chapter 2, and relate to the availability of data and the potential importance of correlation between risks for progression to the different manifestations of decompensated cirrhosis. However, these later stages in the model are less important, for three reasons: (1) a relatively few patients reach these stages; (2) because of high rates of spontaneous presentation over the course of the model, the difference between arms is small; (3) discounting.

Finally, background mortality for the general population was applied to the population of former IDUs. There are no specific estimates for mortality in this population, but it seems likely that if mortality is different, it will be higher in this group. This may introduce a bias in favour of case-finding as long-term benefits may not be realised if the force of background mortality removes people from the non-case-finding cohort before the development of long-term complications of HCV. Cost-effectiveness is less favourable when background mortality risk is doubled, but the value remains well within the range of acceptable cost-effectiveness. The cost-effectiveness of the general case analysis reaches £30,000 per QALY only when mortality is increased to 5.4 times the general population rate.

Impact of alcohol reduction

The inclusion of the effectiveness of alcohol reduction is important as a source of potential benefit for people who are identified through case-finding but ineligible for treatment. Handling of this factor in the model is somewhat simplistic and this may be a limitation. Four factors should be highlighted which, on balance, suggest that the estimate for the contribution of alcohol reduction to the cost-effectiveness of case-finding may be underestimated, that is, greater benefits may be seen in practice than we have estimated.

1. The assumption that a brief counselling intervention would be as effective in former IDUs with HCV as in a general practice population and that change in alcohol intake is maintained throughout the future course of the model. It is difficult to predict what effect this may have on the estimate of cost-effectiveness.
2. The impact of alcohol reduction is restricted to progression of HCV disease. No other benefits of reduced alcohol consumption, including mortality risk in the long-term, are considered. As a result, the value for money of alcohol reduction will have been underestimated.
3. No specific assumptions are made in respect of the utility associated with excessive alcohol intake or its reduction. The impact of this factor is difficult to predict, but it seems likely that the benefits of alcohol reduction may be greater than we have estimated here.
4. Successful reduction in alcohol consumption may lead to some people becoming eligible for treatment. This is not modelled and, again, would make the cost-effectiveness of alcohol reduction advice more favourable.

Comparison with other studies

There have been no further studies of case-finding in the UK since the previous assessment.

Our previous review of cost-effectiveness studies, mainly from the USA, France and Japan, concluded that studies from other health systems are unlikely to be informative for the UK, given differences in disease patterns, clinical practice and health service organisation. We have been unable to find any further assessments of the cost-effectiveness of case-finding published since that time.

One recent French study examined the impact of a consensus conference on GP management of HCV.[105] This showed that only 32% of GPs were aware of the results of two major consensus conferences. There was considerable variation in testing algorithms employed prior to treatment and the authors concluded that "general practitioners were confused concerning the indications for qualitative or quantitative viral RNA investigations". Furthermore, few GPs followed treated HCV-infected patients and renewed interferon prescriptions.

The previous modelling study suggested that case-finding in populations with very low prevalence is unlikely to be cost-effective. The more sophisticated modelling carried out for this assessment confirms this finding. However, the current assessment also suggests that adherence is less important than was suggested by the previous assessment. This is due to several factors. First, the treatment protocol used in this assessment is less reliant on biopsy, which was highlighted as a crucial step in the previous model. Second, the consequences for the non-case-finding cohort were modelled in much more detail than in the previous assessment, in which the consequences of continuing without case-finding and treatment were assumed to be a 10-year delay in presentation with consequent progression. In the current model, people may present at any time. Since people in the non-case-finding arm of the current model are subject to the same assumptions regarding adherence as those in the case-finding arm, the importance of adherence to the incremental analysis is lessened.

Our assessment of the cost-effectiveness of case-finding in drug services is considerably higher than the estimate from the previous study, although it remains less than the presumed threshold for acceptability of £20,000–30,000 per QALY. This is due to the use of more realistic costs for case-finding and the modelling of the comparator arm in this assessment.

Implications for practice

Case-finding for HCV is already supported by national and international guidelines. The current assessment adds weight to these policies by demonstrating that case-finding is likely to be cost-effective.

However, the estimates for cost-effectiveness are not so low that all approaches can unequivocally be considered to represent good value for money. In particular, it has been shown that strategies for case-finding which predominantly identify people early in HCV disease may be less valuable than those which seek to identify people with disease which has already progressed beyond mild hepatitis. This latter group are at higher risk of further progression and therefore stand to gain more from timely intervention.

Conversely, the estimates for cost-effectiveness do not contain much further scope for expenditure in order to realise the expected benefits from treatment. It follows from this that the estimates are less secure for those who may require more support during treatment or whose lifestyle (e.g. continued injecting) carries a risk that benefits will be eroded.

It has been shown that, where a short-term increase in presentation rates is assumed for people approached through case-finding, the results are less uncertain. This suggests that interventions which increase the intensity of case-finding (e.g. systematic follow-up of patients known to be at risk who do not attend for initial testing) may be valuable.

Although the findings suggest that case-finding is cost-effective, we were unable, owing to the striking lack of information, to characterise precisely the configuration of a range of real-world approaches to case-finding. Further empirical work is needed in this area.

Further research

The following areas should be priorities for further research (in priority order):

1. Pilot studies of case-finding strategies are needed, in particular to develop methods of finding people who were infected decades ago

and to evaluate uptake of testing, adherence and effectiveness of treatment.
2. Research into the benefits of case-finding followed by either treatment with combination therapy or approaches to behavioural modification which may result in benefits to infected and non-infected people who are currently injecting drugs.
3. Epidemiological research is needed to (a) monitor the scale and progress of the HCV epidemic and (b) estimate the number and type of IDUs across the UK in a wide range of settings in which case-finding might be considered.
4. Investigation of the effectiveness of harm reduction through advice to reduce alcohol intake in people with HCV is needed.
5. Research into the utility associated with disease states, treatment with combination therapy or counselling to achieve behavioural modification, and sustained viral response in current and former injecting drug users.
6. Studies on the effectiveness and cost-effectiveness of conventional and complementary treatment options such as low-dose PegIFN or dietary interventions, in terms of improving SVR rates and slowing disease progression.
7. Studies on the effect on SVR rates in former IDUs of using hepatitis nurse specialists (under the supervision of experienced consultants) in drug and alcohol units and prisons to improve treatment adherence.
8. Improved estimates of life expectancy in former IDUs.
9. Research into the knowledge and attitudes of clinicians and current and former IDUs towards HCV testing and treatment.
10. Studies on factors which may influence disease progression, such as diabetes and obesity.

Chapter 5
Conclusions

Case-finding for hepatitis C is likely to be considered cost-effective by NHS commissioners. Although there remains considerable uncertainty, particularly around utility values in HCV disease, it appears unlikely that cost-effectiveness would exceed the levels considered acceptable.

Further improvements in the effectiveness of treatments to slow or halt disease progression are likely to improve the cost-effectiveness of case-finding.

Case-finding is likely to be most cost-effective if targeted at people whose HCV disease is likely to be more advanced.

Further empirical work is required to specify, in practice, different approaches to case-finding in appropriate settings and to evaluate their effectiveness and cost-effectiveness directly.

Acknowledgements

We gratefully acknowledge the help of the following: Jo Perry for help with project management and preparation of the manuscript; Professor Howard Thomas and Mr Richard Grieve for providing data from the NHS HTA RCT and cost-effectiveness model of combination therapy for mild hepatitis C; Clare Meachin, Blood Borne Viruses Nurse and Research Sister, and Phil Lewis, Team Manager, Harbour Service (drug and alcohol service), Plymouth, for providing advice on drug and alcohol services and audit data on the acceptance and uptake of HCV testing in Plymouth; and Professor William Irving for providing unpublished data from the Trent Hepatitis C Cohort Database.

Expert advisory group

We are particularly grateful to the following clinical experts, who provided help and advice during the preparation of this assessment: Dr Eleanor Anderson, Specialist Registrar in Public Health Medicine, Lanarkshire; Professor John Campbell, Professor of General Practice, Exeter; Professor Graham Foster, Professor of Hepatology, London; Dr Matthew Hickman, Senior Lecturer in Epidemiology, London; Dr Sharon Hutchinson, Epidemiologist, Glasgow; Professor William Irving, Professor of Virology, Nottingham; Dr Janice Main, Reader in Infectious Diseases, London; Dr David Mutimer, Consultant Hepatologist, Birmingham and Dr Nicholas Pugh, Consultant in Communicable Disease Control, Walsall.

Contribution of authors

Emanuela Castelnuovo (Research Fellow) undertook project management, obtained inputs for the economic model, undertook the design and implementation of the economic model and contributed to report writing. Jo Thompson-Coon (Research Fellow) contributed to the design of the economic model, obtained inputs for the economic model and drafted the report. Martin Pitt (Research Fellow) contributed to model development, verification and interpretation and edited the report. Matthew Cramp (Consultant Hepatologist) contributed to the development of the economic model and edited the report. Uwe Siebert (Assistant Professor) contributed to the development of the economic model and edited the report. Alison Price (Information Scientist) carried out literature searches. Ken Stein (Clinical Senior Lecturer) undertook project management, contributed to the development of the economic model and drafted the report.

References

1. Harris KA, Gilham C, Mortimer PP, Teo CG. The most prevalent hepatitis C virus genotypes in England and Wales are 3a and 1a. *J Med Virol* 1999;**58**:127–31.
2. NIH Consensus Statement online. Management of hepatitis C. NIH Consensus Statement 105 [1997;**15**(3): 1–41. URL: http://odp.od.nih.gov/consensus/cons/105/105-statement.htm
3. Delahooke TE. What is the nature of the problem? *J Viral Hepat* 2004; **11** Suppl 1:5–11.
4. El Serag HB. Hepatocellular carcinoma and hepatitis C in the United States. *Hepatology* 2002;**36**:S74–83.
5. Llovet JM, Bustamante J, Castells A, Vilana R, Del Carmen Ayuso M, Sala M, *et al*. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 1999;**29**:62–67.
6. Freeman AJ, Law MG, Kaldor JM, Dore GJ. Predicting progression to cirrhosis in chronic hepatitis C virus infection. *J Viral Hepat* 2003; **10**:285–93.
7. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet* 1997; **349**:825–32.
8. Dore GJ, Freeman AJ, Law M, Kaldor JM. Natural history models for hepatitis C-related liver disease: different disease progression parameters for different settings. *Antivir Ther* 2003;**8**:365–72.
9. Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C [see comment]. *J Hepatol* 2001;**34**:730–9.
10. Shiffman ML. Natural history and risk factors for progression of hepatitis C virus disease and development of hepatocellular cancer before liver transplantation. *Liver Transpl* 2003;**9**:S14–20.
11. Adinolfi LE, Utili R, Andreana A, Tripodi MF, Rosario P, Mormone G, *et al*. Relationship between genotypes of hepatitis C virus and histopathological manifestations in chronic hepatitis C patients. *Eur J Gastroenterol Hepatol* 2000;**12**:299–304.
12. Roffi L, Redaelli A, Colloredo G, Minola E, Donada C, Picciotto A, *et al*. Outcome of liver disease in a large cohort of histologically proven chronic hepatitis C: Influence of HCV genotype. *Eur J Gastroenterol Hepatol* 2001;**13**:501–6.
13. Verucchi G, Calza L, Manfredi R, Chiodo F. Human immunodeficiency virus and hepatitis C virus coinfection: epidemiology, natural history, therapeutic options and clinical management. *Infection* 2004;**32**:33–46.
14. Sterling RK, Sulkowski MS. Hepatitis C virus in the setting of HIV or hepatitis B virus coinfection. *Semin Liver Dis* 2004;**24** Suppl 2:61–8.
15. Department of Health. *Hepatitis C Strategy for England*. London: Department of Health; 2002.
16. Health Protection Agency. *Supplementary data tables of the Unlinked Anonymous Survey of Injecting Drug Users in contact with services: data to the end of 2003*. London: Department of Health; 2004.
17. Hahn JA, Page-Shafer K, Lum PJ, Bourgois P, Stein E, Evans JL, *et al*. Hepatitis C virus seroconversion among young injection drug users: relationships and risks. *J Infect Dis* 2002; **186**:1558–64.
18. Hay G, McKeganey N, Hutchinson SJ, on behalf of the project team. *Estimating the national and local prevalence of problem drug misuse in Scotland*. London: Health Protection Agency Centre for Infections. Scottish Centre for Infection and Environmental Health. 2001.
19. Bird SM, Hutchinson SJ, Goldberg DJ. Drug-related deaths by region, sex, and age group per 100 injecting drug users in Scotland, 2000–01. *Lancet* 2003;**362**:941–4.
20. Frischer M, Heatlie H, Hickman M. *Estimating the prevalence of problematic and injecting drug use for Drug Action Team areas in England: a feasibility study using the Multiple Indicator Method*. Home Office Online Report 34/04. London: Home Office; 2004.
21. Hickman M, Higgins V, Hope V, Bellis M, Tilling K, Walker A, *et al*. Injecting drug use in Brighton, Liverpool, and London: best estimates of prevalence and coverage of public health indicators. *J Epidemiol Community Health* 2004;**58**:766–71.
22. Johnson AM, Mercer CH, Erens B, Copas AJ, McManus S, Wellings K, *et al*. Sexual behaviour in Britain: partnerships, practices, and HIV risk behaviours. *Lancet* 2001;**358**:1835–42.
23. Bird SM, Goldberg DJ, Hutchinson SJ. Projecting severe sequelae of injection-related hepatitis C virus epidemic in the UK Part 2: preliminary UK estimates of prevalent injection-related hepatitis C carriers, and derivation of progression rates to

liver cirrhosis by gender and age at hepatitis C virus infection. *J Epidemiol Biostat* 2001;**6**:267–77.

24. De Angelis D, Hickman M, Yang S. Estimating long-term trends in the incidence and prevalence of opiate use/injecting drug use and the number of former users: back-calculation methods and opiate overdose deaths. *Am J Epidemiol* 2004; **160**:994–1004.

25. Judd A, Hickman M, Jones S, McDonald T, Parry JV, Stimson GV, *et al*. Incidence of hepatitis C virus and HIV among new injecting drug users in London: a prospective cohort study. *BMJ* 2005;**330**:24–5.

26 . Department of Health. *Hepatitis C Action Plan for England*. London: Department of Health; 2004.

27. Consensus Conference on Hepatitis C. Royal College of Physicians of Edinburgh Consensus Statement. *J Viral Hepat* 2004;**11**(Suppl 1):2–4.

28. EASL International Consensus Conference on Hepatitis C. Paris, 26–28 February 1999, Consensus Statement. European Association for the Study of the Liver. *J Hepatol* 1999;**30**:956–61.

29. Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, *et al*. Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice. *Health Technol Assess* 2002; **6**:(31).

30. Bird SM, Goldberg DJ, Hutchinson SJ. Projecting severe sequelae of injection-related hepatitis C virus epidemic in the UK. Part 1: critical hepatitis C and injector data. *J Epidemiol Biostat* 2001;**6**:243–65.

31. Health Protection Agency, SCIEH, National Public Health Service for Wales, CDSC Northern Ireland, CRDHB, the UASSG. *Shooting up; infections among injecting drug users in the United Kingdom 2003*. London: Health Protection Agency; 2004.

32. Horne JA, Clements AJ, Drennan P, Stein K, Cramp ME. Screening for hepatitis C virus in the Dartmoor prison population: an observational study. *J Public Health* 2004;**26**:372–5.

33. Skipper C, Guy JM, Parkes J, Roderick P, Rosenberg WM. Evaluation of a prison outreach clinic for the diagnosis and prevention of hepatitis C: implications for the national strategy. *Gut* 2003;**52**:1500–4.

34. Department of Health. *Models of care for the treatment of drug misusers; 2002*. London: National Treatment Agency for Substance Misuse; 2002.

35. Wong J, Sylvestre D, Siebert U. Cost-effectiveness of treatment of hepatitis C in injecting drug users. In Jager J, Limburg W, Kretzschmar M, Postma M, Wiessing L, editors. *Hepatitis C and injecting drug use: impact, costs and policy options*. EMCDDA, Vol. 7. Lisbon: European Monitoring Centre for Drugs and Drug Addiction; 2004. pp. 219–41.

36. Colin C, Lanoir D, Touzet S, Meyaud-Kraemer L, Bailly F, Trepo C. Sensitivity and specificity of third-generation hepatitis C virus antibody detection assays: an analysis of the literature. *J Viral Hepat* 2001;**8**:87–95.

37. Booth JC, O'Grady J, Neuberger J. Clinical guidelines on the management of hepatitis C. *Gut* 2001;**49** Suppl 1:I1–21.

38. Ishak K, Baptista A, Bianchi L, Callea F, De GJ, Gudat F, *et al*. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995;**22**:696–9.

39. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology* 1996;**24**:289–93.

40. Cadranel JF, Rufat P, Degos F. Practices of liver biopsy in France: results of a prospective nationwide survey. For the Group of Epidemiology of the French Association for the Study of the Liver (AFEF). *Hepatology* 2000;**32**:477–81.

41. Shepherd J, Waugh N, Hewitson P. Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review. *Health Technology Assessment* 2004;**4**(33).

42. Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J. Pegylated interferon alpha-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess* 2004;**8**:1–140.

43. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman ML, Reindollar R, *et al*. Peginterferon alfa-2b plus ribavirin compared with interferon alfa 2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;**358**:958–65.

44. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL, *et al*. Peginterferon alfa 2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;**347**:975–82.

45. Wright M, Forton D, Main J, Goldin R, Torok E, Tedder R, *et al*. Treatment of histologically mild hepatitis C virus infection with interferon and ribavirin: a multicentre randomized controlled trial. *J Viral Hepat* 2005;**12**:58–66.

46. Chou R, Clark EC, Helfand M. Screening for hepatitis C virus infection: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2004;**140**:456–79.

47. Camma C, Giunta M, Andreone P, Craxi A. Interferon and prevention of hepatocellular carcinoma in viral cirrhosis: an evidence based approach. *J Hepatol* 2001; **34**:593–602.

48. Thompson Coon J, Ernst E. Complementary and alternative therapies in the treatment of chronic hepatitis C: a systematic review. *J Hepatol* 2004; **40**:491–500.

49. Testa G, Crippin JS, Netto GJ, Goldstein RM, Jennings LW, Brkic BS, *et al*. Liver transplantation for hepatitis C: recurrence and disease progression in 300 patients. *Liver Transpl* 2000;**6**:553–61.

50. Neumann UP, Berg T, Bahra M, Puhl G, Guckelberger O, Langrehr JM, *et al*. Long-term outcome of liver transplants for chronic hepatitis C: a 10-year follow-up. *Transplantation* 2004; **77**:226–31.

51. Firpi RJ, Abdelmalek MF, Soldevila-Pico C, Cabrera R, Shuster JJ, Theriaque D, *et al*. One-year protocol liver biopsy can stratify fibrosis progression in liver transplant recipients with recurrent hepatitis C infection. *Liver Transpl* 2004;**10**:1240–7.

52. Freeman AJ, Dore GJ, Law MG, Thorpe M, Von Overbeck J, Lloyd AR, *et al*. Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology* 2001;**34**:809–16.

53. McCusker M. Influence of hepatitis C status on alcohol consumption in opiate users in treatment. *Addiction* 2001;**96**:1007–14.

54. Gallegos-Orozco JF, Fuentes AP, Gerardo AJ, Perez-Pruna C, Hinojosa-Becerril C, Sixtos-Alonso MS, *et al*. Health-related quality of life and depression in patients with chronic hepatitis C. *Arch Med Res* 2003;**34**:124–9.

55. Bonkovsky HL, Woolley JM. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy. The Consensus Interferon Study Group. *Hepatology* 1999;**29**:264–70.

56. Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. *Hepatology* 1998;**27**:209–12.

57. Cordoba J, Flavia M, Jacas C, Saudela S, Esteban JI, Vargas V, *et al*. Quality of life and cognitive function in hepatitis C at different stages of liver disease. *J Hepatol* 2003;**39**:231–8.

58. Chong CA, Gulamhussein A, Heathcote EJ, Lilly L, Sherman M, Naglie G, *et al*. Health-state utilities and quality of life in hepatitis C patients. *Am J Gastroenterol* 2003;**98**:630–8.

59. Siebert U, Ravens-Sieberer U, Greiner W, Sroczynski G, Wong JB, Kuntz KM, *et al*. Performance of different utility assessment methods in chronic hepatitis C patients. In Kind P, Macran S, editors. *Discussion papers*. Centre for Health Economics, University of York: York; 2003.

60. van der Plas SM, Hansen BE, de Boer JB, Stijnen T, Passchier J, de Man RA, *et al*. Generic and disease specific health related quality of life in non-cirrhotic, cirrhotic and transplanted liver patients: a cross-sectional study. *BMC Gastroenterol* 2003;**3**:33.

61. McHutchison JG, Ware JE Jr, Bayliss MS, Pianko S, Albrecht JK, Cort S, *et al*. The effects of interferon alpha-2b in combination with ribavirin on health related quality of life and work productivity. *J Hepatol* 2001;**34**:140–7.

62. Dalgard O, Egeland A, Skaug K, Vilimas K, Steen T. Health-related quality of life in active injecting drug users with and without chronic hepatitis C virus infection. *Hepatology* 2004;**39**:74–80.

63. Loge JH, Kaasa S. Shortform 36 (SF-36) health survey: normative data from the general Norwegian population. *Scand J Soc Med* 1998;**26**:250–8.

64. Weild AR, Gill ON, Bennett D, Livingstone SJ, Parry JV, Curran L. Prevalence of HIV, hepatitis B, and hepatitis C antibodies in prisoners in England and Wales: a national survey. *Commun Dis Public Health* 2000;**3**:121–6.

65. Lamden KH, Kennedy N, Beeching NJ, Lowe D, Morrison CL, Mallinson H, *et al*. Hepatitis B and hepatitis C virus infections: risk factors among drug users in Northwest England. *J Infect* 1998;**37**:260–9.

66. Majid A, Holmes R, Desselberger U, Simmonds P, McKee TA. Molecular epidemiology of hepatitis C virus infection amongst intravenous drug users in rural communities. *J Med Virol* 1995;**46**:48–51.

67. Mohsen AH, Group TH, Trent HCV Study Group. The epidemiology of hepatitis C in a UK health regional population of 5.12 million. *Gut* 2001; **48**:707–13.

68. Cramp ME, Rosenberg W. Guidance on the treatment of hepatitis C incorporating the use of pegylated interferons. London: British Society for Gastroentrology; 2003. URL: http://www.bsg.org.uk/pdf_word_docs/pegylated_2003.doc

69. Irving WL. The role of the virology laboratory in the management of hepatitis C virus infection. *J Clin Virol* 2002;**25**:3–13.

70. Serfaty M, Lawrie A, Smith B, Brind AM, Watson JP, Gilvarry E, *et al*. Risk factors and medical follow-up of drug users tested for hepatitis C – can the risk of transmission be reduced? *Drug Alcohol Rev* 1997;**16**:339–47.

71. Jowett SL, Agarwal K, Smith BC, Craig W, Hewett M, Bassendine DR, *et al*. Managing chronic hepatitis C acquired through intravenous drug use. *Qjm* 2001;**94**:153–8.

72. Smyth BP, Keenan E, O'Connor JJ. Assessment of hepatitis C infection in injecting drug users attending an addiction treatment clinic. *Ir J Med Sci* 2000;**169**:129–32.

73. Tiffen L, Sheridan S. Improving take-up of hepatitis C services. *Nurs Times* 2002;**98**(43): 30–32.

74. Poynard T, Ratziu V, Bedossa P. Appropriateness of liver biopsy. *Can J Gastroenterol* 2000;**14**: 543–8.

75. Foster GR, Goldin RD, Main J, Murray-Lyon I, Hargreaves S, Thomas HC. Management of chronic hepatitis C: clinical audit of biopsy based management algorithm. *BMJ* 1997;**315**:453–8.

76. National Institute of Clinical Excellence. *Interferon alfa (pegylated and non pegylated) and ribavirin for the treatment of chronic hepatitis C.* Technology Appraisal 75. London: NICE; 2004.

77. Beich A, Thorsen T, Rollnick S. Screening in brief intervention trials targeting excessive drinkers in general practice: a systematic review and meta-analysis. *BMJ* 2003;**327**:536–43.

78. Wright M, Grieve R, Roberts J, Main J, Thomas H, on behalf of the UK mild hepatitis C trial investigators. Health benefits of anti-viral therapy for mild chronic hepatitis C. *Health Technol Assess* 2006;**10**(21).

79. Dore GJ, Freeman AJ, Law M, Kaldor JM. Is severe liver disease a common outcome for people with chronic hepatitis C? *J Gastroenterol Hepatol* 2002;**17**:423–30.

80. Romeo R, Colombo M, Rumi M, Soffredini R, Del NE, Donato MF, *et al*. Lack of association between type of hepatitis C virus, serum load and severity of liver disease. *J Viral Hepat* 1996; **3**:183–90.

81. Niederau C, Lange S, Heintges T, Erhardt A, Buschkamp M, Hurter D, *et al*. Prognosis of chronic hepatitis C: results of a large prospective cohort study. *Hepatology* 1998;**28**:1687–95.

82. Benvegnu L, Noventa F, Bernardinello E, Pontisso P, Gatta A, Alberti A. Evidence for an association between the aetiology of cirrhosis and pattern of hepatocellular carcinoma development. *Gut* 2001;**48**:110–5.

83. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, *et al*. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997;**112**:463–72.

84. Fattovich G, Giustina G, Degos F, Diodati G, Tremolada F, Nevens F, *et al*. Effectiveness of interferon alfa on incidence of hepatocellular carcinoma and decompensation in cirrhosis type C. *J Hepatol* 1997;**27**:201–5.

85. Fattovich G, Pantalena M, Zagni I, Realdi G, Schalm SW, Christensen E. Effect of hepatitis B and C virus infections on the natural history of compensated cirrhosis: a cohort study of 297 patients. *Am J Gastroenterol* 2002;**97**:2886–95.

86. Benvegnu L, Alberti A. Patterns of hepatocellular carcinoma development in hepatitis B virus and hepatitis C virus related cirrhosis. *Antiviral Res* 2001;**52**:199–207.

87. Bruno S, Silini E, Crosignani A, Borzio F, Leandro G, Bono F, *et al*. Hepatitis C virus genotypes and risk of hepatocellular carcinoma in cirrhosis: a prospective study. *Hepatology* 1997; **25**:754–8.

88. Serfaty L, Aumaitre H, Chazouilleres O, Bonnand A, Rosmorduc O, Poupon RE, *et al*. Determinants of outcome of compensated hepatitis C virus related cirrhosis. *Hepatology* 1998;**27**:1435–40.

89. Degos F, Christidis C, Ganne-Carrie N, Farmachidi J-P, Degott C, Guettier C, *et al*. Hepatitis C virus related cirrhosis: time to occurrence of hepatocellular carcinoma and death. *Gut* 2000;**47**:131–6.

90. Transplant UK, Statistics and Audit Directorate. *Transplant activity in the UK, 2003–2004*. London: Transplant UK, Statistics and Audit Directorate; 2004.

91. Rodriguez-Luna H, Douglas DD. Natural history of hepatitis C following liver transplantation. *Cur Opin Infect Dis* 2004;**17**:363–71.

92. Neumann UP, Berg T, Bahra M, Seehofer D, Langrehr JM, Neuhaus R, *et al*. Fibrosis progression after liver transplantation in patients with recurrent hepatitis C. *J Hepatol* 2004;**41**:830–6.

93. Planas R, Balleste B, Alvarez MA, Rivera M, Montoliu S, Galeras JA, *et al*. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. *J Hepatol* 2004; **40**:823–30.

94. Office for National Statistics. *Cancer statistics registrations: registrations of cancer diagnosed in 2001, England. Series MB1 No*. 32. London: Office for National Statistics; 2004.

95. *Office for National Statistics. Consumer Prices Index (CPI) 1988–2004, Monthly, First/News/Press Release*, On-line edition. London: Office for National Statistics; 2004.

96. Home Office. *Prison statistics England and Wales*. Cm 5996. London: Home Office; 2002.

97. Edeh J, Spalding P. Screening for HIV, HBV and HCV markers among drug users in treatment in rural south-east England. *J Public Health Med* 2000;**22**:531–9.

98. Curtis L, Netten A. *Unit costs of health and social care 2004*. Canterbury: Personal Social Services Research Unit; 2004.

99. *British National Formulary*. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain; 2004.

100. Ratcliffe J, Longworth L, Young T, Bryan S, Burroughs A, Buxton M. Assessing health-related quality of life pre- and post-liver transplantation: a prospective multicenter study. *Liver Transpl* 2002;**8**:263–70.

101. Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S. A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment Programme. *Health Technol Assess* 2004;**8**(31).

102. Brennan A, Kharroubi S, O'Hagan A, Chilcott J. Calculating partial expected value of perfect information in cost-effectiveness models. School of Health and Related Research (ScHARR), University of Sheffield, 2002 (www.shef.ac.uk/content/1/c6/02/96/05/Brennan.doc).

103. Kaur S, Rybicki LB, Bacon B, Gollan J, Rustgi V, Carey W. Performance characteristics and results of a large-scale screening programme for viral hepatitis and risk factors associated with exposure to viral hepatitis B and C: results of the National Hepatitis Screening Survey. *Hepatology* 1996;**24**:979–86.

104. Gore SM, Bird AG, Cameron SO, Hutchinson SJ, Burns SM, Goldberg DJ. Prevalence of hepatitis C in prisons: WASH-C surveillance linked to self-reported risk behaviours. *QJM* 1999;**92**: 25–32.

105. Ouzan D, Hofliger P, Cavailler P, Mamino C, Tran A. Screening and hepatitis C management survey in general medicine in the Alpes-Maritime and East Var area. *Gastroenterol Clin Biol* 2003;**27**:90–3.

Appendix 1

Search strategies and sources

Five separate systematic searches were undertaken to obtain parameters for the decision analytic model. Published literature was identified from the following electronic and Internet sources and the MEDLINE strategies below were adapted to run in the range of databases.

- electronic databases, including MEDLINE, PreMEDLINE, EMBASE, The Cochrane Library (including the Cochrane Systematic Review Database, Cochrane Central Register of Controlled Trials), CRD HTA, DARE, NHS EED databases, Econlit
- websites of regulatory agencies (e.g. FDA, EMEA and MHRA)
- websites of the Professional Groups such as BASL, EASL and the Advisory Group on Hepatitis (AGH) and any associated databases
- websites of the UK Department of Health, Health Protection Agency, Office for National Statistics
- websites of manufacturers of health technologies for HCV
- research groups or other groups with special interest in HCV prevention and treatment identified through literature searches and contact with experts
- websites of patients' associations (Hepatitis C Trust, British Liver Trust).

Natural history

MEDLINE (OVID)1996–October week 4, 2004

1. (hepatitis C or hcv).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
2. exp Hepatitis C/ or Hepatitis C, Chronic/ or exp Hepacivirus/
3. or/1-2
4. exp Disease Progression/
5. exp Markov Chains/
6. exp models, biological/ or exp models, statistical/
7. 5 or 6
8. 4 and 7
9. exp Liver Cirrhosis/pa, di, et, vi [Pathology, Diagnosis, Etiology, Virology]
10. exp risk factors/
11. 9 and 10
12. 8 or 11
13. 12 and 3
14. limit 13 to (human and english language)

Acceptability of testing procedures and adherence to treatment

MEDLINE (OVID)1996–October week 4, 2004

1. exp Substance Abuse, Intravenous/
2. (inject$ adj3 drug$ use$).mp.
3. (intravenous adj3 drug$ use$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4. (intravenous adj3 drug abuse$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
5. (IDU$ or IVDU$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
6. ((injecting or injection) and drug user$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7. or/1-6
8. (hepatitis C or hcv).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
9. exp Hepatitis C/ or Hepatitis C, Chronic/ or exp Hepacivirus/
10. or/8-9
11. (screen$ or test$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
12. exp Mass Screening/
13. (ELISA or enzyme linked immunosorbant assay).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
14. (PCR or polymerase chain reaction).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
15. (OFT or oral fluid testing).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
16. (RIBA or recombinant immunoblot assay).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

17. exp Biopsy/
18. liver biopsy.mp.
19. 17 and liver.mp.
20. or/11-16,18-19
21. 10 and 20
22. 21 and 7
23. exp Medical Audit/
24. exp "Patient Acceptance of Health Care"/
25. (uptak$ or adheren$ or complian$ or concord$ or accept$ or audit$ or "right$ of test$").ti.
26. patient compliance/ or treatment refusal/
27. exp algorithms/
28. or/23-27
29. 28 and 21
30. 7 and 10
31. 30 and 28
32. 25 and 10
33. 29 or 31 or 32
34. limit 33 to english language

Effectiveness of treatment

MEDLINE (OVID)1996–October week 4, 2004

1. (hepatitis C or hcv).mp. [mp=title, original title, abstract,name of substance, mesh subject heading]
2. exp Hepatitis C/ or Hepatitis C, Chronic/ or exp Hepacivirus/
3. or/1-2
4. (pegylated or pegasys or peg$ or polyethylene glycol or pegintron or rebetron or peginterferon or peg-interferon).mp.
5. (ribav#rin or rebetol).mp.
6. Ribavirin/
7. 5 or 6
8. 4 and 7
9. 8 and 3
10. limit 9 to (english language and yr=2003-2004)

Costs of long-term treatment and complications of HCV

MEDLINE (OVID)1996–November Week 1, 2004

1. (hepatitis C or hcv).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
2. exp Hepatitis C/ or Hepatitis C, Chronic/ or exp Hepacivirus/
3. or/1-2
4. Liver Cirrhosis/co, ec, ep, su, th, et [Complications, Economics, Epidemiology, Surgery, Therapy, Etiology]
5. 4 and 3
6. 3 or 5
7. exp "costs and cost analysis"/
8. Cost-Benefit Analysis/
9. exp Health Care Costs/
10. 7 or 8 or 9
11. 10 and 6
12. limit 11 to (english language and yr=2001-2004)

Quality of life

MEDLINE (OVID) 1996 to November Week 1, 2004

1. value of life/
2. quality adjusted life year/
3. quality adjusted life.ti,ab.
4. (qaly$ or qald$ or qale$ or qtime$).ti,ab.
5. disability adjusted life.ti,ab.
6. daly$.ti,ab.
7. health status indicators/
8. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.
9. (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.
10. (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.
11. (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.
12. (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.
13. (euroqol or euro qol or eq5d or eq 5d).ti,ab.
14. (hql or hqol or h qol or hrqol or hr qol).ti,ab.
15. (hye or hyes).ti,ab.
16. health$ year$ equivalent$.ti,ab.
17. health utilit$.ab.
18. (hui or hui1 or hui2 or hui3).ti,ab.
19. disutil$.ti,ab.
20. rosser.ti,ab.
21. quality of well being.ti,ab.
22. quality of wellbeing.ti,ab.
23. qwb.ti,ab.
24. willingness to pay.ti,ab.
25. standard gamble$.ti,ab.
26. time trade off.ti,ab.
27. time tradeoff.ti,ab.
28. tto.ti,ab.
29. (index adj2 well being).mp.
30. (quality adj2 well being).mp.

31. (health adj3 utilit$ ind$).mp. [mp=title, original title,abstract, name of substance, mesh subject heading]
32. ((multiattribute$ or multi attribute$) adj3 (health ind$ or theor$ or health state$ or utilit$ or analys$)).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
33. quality adjusted life year$.mp.
34. (15D or 15 dimension$).mp.
35. (12D or 12 dimension$).mp.
36. rating scale$.mp.
37. linear scal$.mp.
38. linear analog$.mp.
39. visual analog$.mp.
40. (categor$ adj2 scal$).mp.
41. or/1-40
42. (letter or editorial or comment).pt.
43. 41 not 42
44. (hepatitis C or hcv).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
45. exp Hepatitis C/ or Hepatitis C, Chronic/ or exp Hepacivirus/
46. 44 or 45
47. 46 and 43
48. limit 47 to (english language and yr=2001 – 2004)

Appendix 2
Protocol

Details of review team (affiliations and contributions) are given on the title page and in the Acknowledgements.

Full title of research question

What is the clinical effectiveness and cost-effectiveness of testing for hepatitis C virus (HCV) in former injecting drug users?

Clarification of the research question and scope

Background

Hepatitis C infects up to 1% of the general population and prevalence may be as high as 90% in some groups of IDUs. Infection is characterised by a high probability of chronicity and, after a long but variable latent period, important long-term clinical manifestations. These are cirrhosis, which may lead to liver failure (leading to ascites, oesophageal varices, encephalopathy and the need for transplantation) and HCC. Advanced stages of liver disease are associated with poor QoL and an increased mortality risk.

The parenteral route is much more important than other means of transmission (e.g. sexual intercourse). Prior to the advent of effective screening of blood products, many infections were acquired iatrogenically but currently the group at highest risk are IDUs. Co-infection with other viruses, notably hepatitis B and HIV, in this population is not uncommon.

Symptoms of chronic hepatitis due to HCV are variable and people may not present to services until liver disease is relatively advanced. Given the long latent period, this suggests a role for finding asymptomatic cases amenable to treatment. Case-finding may be opportunistic (e.g. in populations with low prevalence such as general practice) or targeted on high-risk populations (e.g. in drug treatment services or prisons).

Although a range of initial and confirmatory diagnostic test combinations is available, the preferred approach in the UK is for ELISA antibody testing to be followed by PCR confirmation of infection and liver biopsy to stage disease. Treatment for moderate to severe chronic HCV, using combination therapy of PegIFN and ribavirin, is recommended in professional guidelines in the UK and overseas. Research is also becoming available on treating mild chronic hepatitis. Treatment may not be recommended for a proportion of those with infection due to stage of liver disease, co-morbidity (such as psychiatric illness) and ongoing injecting drug use. However, case-finding may still be considered worthwhile in such groups in order to promote behavioural change aimed at (a) reducing the rate of progression of liver disease through reducing alcohol use and (b) preventing further spread of the virus by stopping the sharing of drug paraphernalia.

The previous HTA carried out by the Peninsula Technology Assessment Group considered case-finding in two settings: drug treatment services and GUM clinics. The assessment included a review of behavioural change in response to the diagnosis of HCV and a survey of current practice in NHS drug treatment and GUM services. The cost-effectiveness of case-finding was estimated using a decision analytic model and suggested that systematic case-finding in drug treatment services was likely to be considered cost-effective, whereas the case for GUM service was less certain. Many uncertainties were identified in the study, which suggested the need for more sophisticated modelling.

This Technology Assessment Report (TAR) will update and extend the modelling study carried out in the previous assessment. Following the convention of the UK National Screening Committee, the term 'case-finding' is used in preference to 'screening' as the population of interest already has a health problem – investigation of HCV state is contingent on establishing a history of injecting drug use.

Scope and aim

The TAR will assess the cost-effectiveness of testing for HCV infection in adults with a history of injecting drug use. In people who are eligible for, and concordant with antiviral therapy,

treatment with combination therapy (PegIFN and ribavirin) will be assumed. In people who are not eligible, the potential benefits of case-finding through alcohol restriction and changes in sharing of drug paraphernalia will be explored.

The aims of the TAR are therefore to:

- estimate the impact of testing for and treating HCV on mortality and morbidity from chronic HCV
- determine the impact of testing for HCV on duration and QoL of IDUs, in terms of QALYs
- estimate the costs associated with testing and treatment and the consequent cost-effectiveness and cost–utility of testing and treatment, making uncertainty in the estimates explicit
- in people who are ineligible for treatment, but not currently injecting drugs, estimate the impact on disease progression of reducing alcohol intake
- in people who are currently IDUs, estimate the impact of case-finding on transmission of HCV due to changes in behaviour arising from knowledge of HCV status
- consider the implications for service provision in the NHS and other sectors.

The TAR will update and extend the previous assessment report on screening in GUM and IDU services.[1] Building on the previous modelling study, the present TAR will:

- Re-focus the research question from the setting of delivery (GUM clinics) to the population group at highest risk of infection (IDUs) and consider the impact of case-finding in this group in a range of settings.
- Include recent changes in standard treatment (i.e. combination therapy with PegIFN and ribavirin).
- Improve the structure of the model to investigate cost-effectiveness in a wider range of specific populations according to, for example, age, viral load, viral genotype, severity of hepatitis and co-infection with other viruses.
- Carry out a more exhaustive review of treatment adherence and other parameters shown to be particularly important in the previous modelling study.
- Improve the analysis of uncertainty through incorporation of probabilistic sensitivity analysis and estimation of EVPI from the model.
- Consider the impact of alcohol reduction on progression and, if possible, the impact of changes in needle sharing behaviours on transmission. However, these elements of the assessment will be second-order priorities given (a) the restricted time available for the study and (b) the potential difficulties involved in obtaining appropriate data for modelling purposes.

Specification of population, interventions, comparators and outcomes of interest

Population

Adults (age 18+ years) with a history of injecting drug use. The population will be stratified, if possible, according to

- age
- viral genotype
- viral load
- severity of liver disease
- co-infection – HIV or HBV
- previous treatment with earlier 'standard' treatments for HCV
- injecting history – past or current.

The main population of interest is those people considered eligible for treatment with combination therapy. Eligibility will be defined by current treatment guidelines in the UK[2,3] and in consultation with the Expert Advisory Group. Where possible, the treatment-eligible population will be stratified according to the likely prevalence of factors determining response to treatment (age, viral factors, previous treatment) and factors that may influence long-term survival (and therefore the benefit of treatment for HCV, which is the avoidance of long-term consequences of infection).

People who are currently injecting drugs are not considered eligible for antiviral hepatitis C treatment in the UK. If data and resources are available, we will investigate the possible impact of testing and treatment on this group as part of the study by exploring simple hypotheses on the impact of reinfection. However, it will be beyond the scope of the current assessment to model the potential impact of treatment on infection dynamics in the entire population.

Intervention

Case-finding and treatment represent a complex intervention involving several types of health technology. Offering testing to people without current symptoms is a health promotion intervention and may take a wide range of formats depending on the setting. Specifying the type of approach will not be considered in detail in this

study, although uptake on initial approach is likely to be an important determinant of overall effectiveness and will be considered.

Diagnostic technologies are required for initial antibody testing (ELISA), viral studies (PCR) and disease staging (liver biopsy). This sequence of investigation is supported by national and international clinical guidelines[2,4] and is the most common approach used in the UK. Therefore, we do not propose to investigate the impact of other investigations on cost-effectiveness, although this will be confirmed with the Expert Advisory Group early in the project.

Pharmaceutical intervention, in people considered eligible, will be with standard doses of PegIFN combined with ribavirin, administered according to treatment protocols considered to represent best clinical practice by members of the Expert Advisory Group.

Comparator

In the absence of testing, it will be assumed that the natural history of HCV infection will occur in untreated individuals. Management of longer term complications will occur as patients are detected, either through clinical symptoms or diagnostic makers in routine exams (e.g. elevated ALT levels). In most cases, this will be following the onset of more serious long term consequences of HCV infection (e.g. cirrhosis, liver failure and HCC). Treatment for these states will follow current clinical practice and may include liver transplant.

Outcomes

A range of outcomes will be estimated, where underlying data permit:

- yield of case-finding: the number of cases of sustained viral response obtained as a proportion of the number of people invited for testing
- harms of testing and treatment, i.e. adverse effects of interventions such as liver biopsy or combination therapy
- LYGs
- QALYs gained (using, where possible, societal estimates of utility weights based on descriptions of relevant health states obtained from sufferers).

Costs associated with testing, treatment and the long-term sequelae of infection will be estimated, allowing estimation of total and incremental costs of different strategies.

Incremental cost-effectiveness and cost–utility will be estimated.

Study methods

Methods for estimating QoL, costs and cost-effectiveness and/or cost per QALY

Developing model structure

The decision analytic model will compare the costs and outcomes of case-finding over the long term, compared with no case-finding, from the perspective of a third-party payer in the UK (NHS). The model will be developed in Microsoft Excel. It will be based on our previous work[1] (*Figures 18* and *19*, taken from the previous cost–utility model) and will integrate a model of invitation, testing, diagnosis and staging with a Markov model of natural history which forms the basis for estimating the benefits of treatment.

Some structural features of the previous model will be refined to incorporate additional strategies, such as the opportunistic treatment of individuals, eligible for treatment, who have been identified outside case-finding. In the base case, this option will be incorporated in the no-case-finding strategy and its impact will be assessed using relevant parameters, retrieved from literature or elicited from experts. Relapse or reinfection rates in the long term will be added following successful sustained viral response after treatment.

The model structure will be developed in consultation with the Expert Advisory Group.

Outputs

The main output will be incremental cost per QALY. The costs and consequences of different options will also be presented, as will the cost to achieve/prevent clinically important, disease specific states such as sustained viral responder, cirrhosis or HCC.

Time frame

The time frame for the model needs to be long enough for the stream of costs and consequences associated with HCV infection to become manifest. This will require estimates of the nature of the population eligible for testing and the likely natural history of the disease. The model will therefore cover the expected lifespan of the cohort and so will be long term (decades). The precise duration will be specified during model development, according to the findings of the initial literature review, particularly on life expectancy in people with a history of injecting drug use.

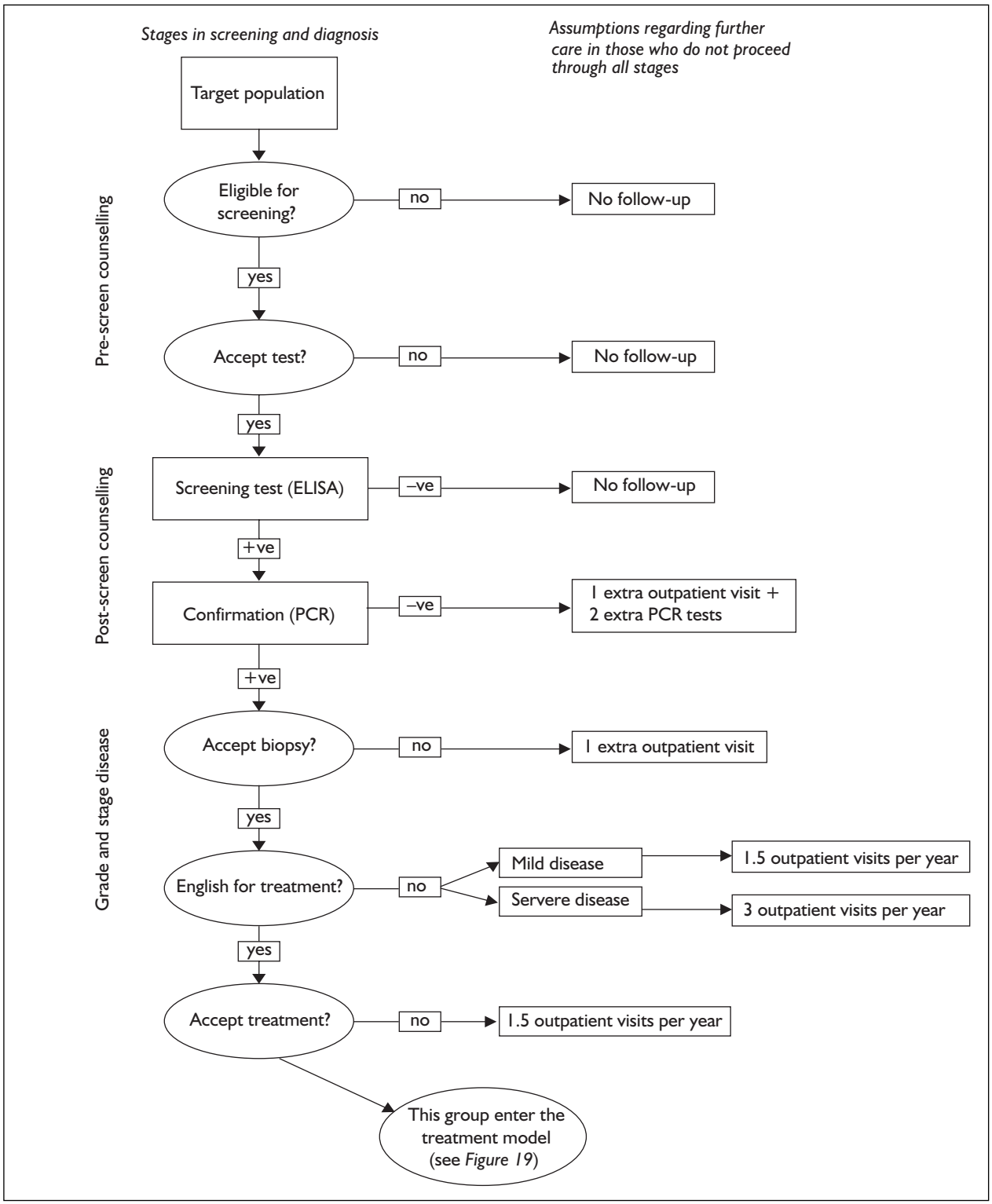


FIGURE 18 *Model of screening, taken from the previous HTA report*[1]

Effectiveness

Effectiveness of case-finding will be determined based on the expected value of all health outcomes prevented with case-finding over the course of the period modelled.

Acceptability of case-finding

Acceptability of case-finding will be explicitly modelled using estimates of rates of compliance or dropout from the various stages of testing and of treatment. We will seek appropriate estimates from

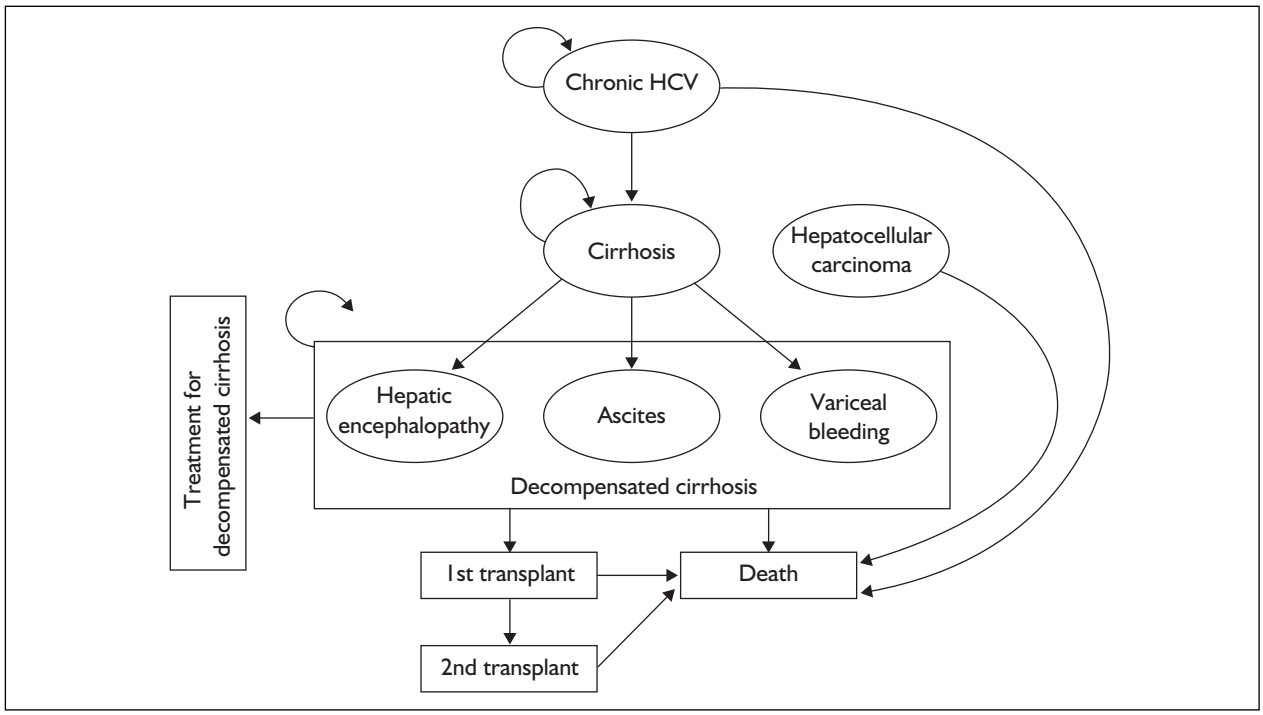


FIGURE 19 *Model of treatment, taken from the previous HTA report*[1]

the literature and by consultation with the Expert Advisory Group.

If possible, within the time constraints placed on the project, we will also seek qualitative data on attitudes towards HCV and testing for it among people with a history of injecting drug use.

Costs

Estimates for resource use at each stage of the model will be obtained from the literature and in consultation with the Expert Advisory Group or other nominated experts. Resources will be valued using routine sources (e.g. PSSRU and NHS Reference Costs) where possible. Technology prices will be obtained from the BNF, manufacturers and, in some circumstances, selected NHS Trusts.

Costs will be calculated from the perspective of the public sector organisations: the NHS, Personal Social Services and, where appropriate, HM Prisons and will be discounted at 3.5% per year.

Benefits

Health benefits due to case-finding include an increase in life expectancy and an improvement in health-related QoL. The Markov process will require application of QoL (utility) weights to the time spent in the health states modelled in order to calculate QALYs. Ideally, these should reflect the preferences of the general public to the health states concerned. That is, they should be elicited from a representative sample of the general population using techniques that yield an estimate of preference strength under uncertainty. Descriptions of the health states should be derived from people whose condition represents the health states of interest in the model.

Benefits will be discounted at 3.5% per year.

Sources of input parameters

The approach to obtaining values for model parameters will be similar to that used in literature reviews. Values for model parameters will be retrieved from published or unpublished literature. Relevant papers will be identified by searching electronic resources (listed in the last section of this Appendix), inspecting reference lists and contact with manufacturers of technologies and experts in the field via the Expert Advisory Group.

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, we will make definition of questions and subsequent searches as explicit as possible.

Studies will be selected if they provide best evidence around key parameters for the model. In general, studies will be first selected based on key methodological characteristics in relation to each parameter.

For progression of HCV-related disease over the medium or long term, the best studies will be recent, large cohorts, measuring progression using appropriate outcomes as included in the model (i.e. time to progression to fibrosis and cirrhosis, decompensated cirrhosis, incidence of HCC, liver transplant rates and death).

The effectiveness and harms of treatment with PegIFN and ribavirin will be extracted from published systematic reviews or meta-analyses. Where possible, pooled results will be used to inform the model. In the absence of published syntheses of effectiveness, RCTs will be selected and, where possible, synthesised using meta-analysis. Cohort or longitudinal studies may be considered for longer term outcomes after treatment, if this information is not available from controlled studies.

For the effectiveness of treatment, studies will be selected if they included participants with the current eligibility criteria for treatment in the UK, that is, moderate to severe liver fibrosis. Studies of effectiveness in people with other grades of liver disease (e.g. mild) may be used to inform alternative treatment scenarios.

For some parameters, it is expected that RCTs are less likely to be available or appropriate. For the effect of behavioural interventions on risk behaviour, acceptability of testing and/or adherence to treatment and the proportion of patients with history of previous treatment, data will be sought from cross-sectional or longitudinal uncontrolled studies, according to the type of parameter.

For all parameters, preference will be given to studies conducted in the UK IDU population. Studies from other countries or conducted in other HCV-infected populations may be used if they constitute best available evidence. In all cases we will provide the rationale for choosing model input values.

Model validation and verification

Validation means the extent to which the model represents the disease process adequately. The performance of the model will be assessed, comparing model outputs with other models of disease progression and with cohort studies of disease progression.

Model verification refers to efforts to reduce the error rate within the model. We will adhere to internal protocols regarding model programming, which include using only one modeller to programme the file, ongoing checks of model performance, maintenance of a log of queries and changes to the model. Finally, the model will be made available for scrutiny and comment to the project's external reviewers.

Analysis of uncertainty

The model will use one-way sensitivity analysis to identify input variables which have, across a plausible range, the greatest impact on outputs. These will be subject, where possible, to more intensive searching for evidence.

Probabilistic sensitivity analysis will be used to investigate the combined effect of uncertainty across all parameters. In this approach, each input data value is drawn from a probability distribution, chosen according to the nature of the data and plausible estimates for range and shape, and the model run at least 1000 times. The main outputs of the analysis are graphical: incremental cost-effectiveness planes and CEACs. These indicate the probability of a strategy being considered cost-effective given a range of values which society may be willing to pay for an additional outcome (in this case, a QALY).

The probabilistic sensitivity analysis will also facilitate calculation of the EVPI from the model. This is the upper bound on the value of reducing all decision uncertainty to zero, that is, the maximum amount which might justifiably be spent on further research. If resources permit, it may be possible to calculate the pEVPI, which indicates the maximum value of reducing uncertainty in each parameter.

Structural uncertainty will be explored using scenarios to modify key assumptions and determinants of cost-effectiveness.

In the base case, the model assumes that individuals successfully treated will remain healthy in the longer term, that is, treated individuals will achieve complete health over the long term. If time permits, the impact of relaxing this assumption will be tested in a sensitivity analysis.

Project management

Timetable/milestones

- draft protocol: 5 November 2004
- final protocol: 25 November 2004
- progress report to NCCHTA: 15 April 2005
- submission of final report: 27 May 2005.

Competing interests

See the title page.

External review

An Expert Advisory Group is currently being formed, which will act as an expert resource through production of the assessment.

In addition, the Report will be subject to external review by at least two experts acting on behalf of the NHS HTA Programme. These referees will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. An external methodological referee will be asked to review the report and scrutinise the decision analytic model. Referees will review a complete and near final draft of the assessment report and will understand that their role is part of external quality assurance. The Advisory Group and referees will be required to sign a copy of the HTA Programme's C*onfidentiality Acknowledgement and Undertaking*, which we will hold on file.

Comments from referees, together with our responses, will be made available to NCCHTA in strict confidence for editorial review and approval.

References

1. Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, *et al*. Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice. *Health Technol Assess* 2002;**6**(31).
2. Booth JC, O'Grady J, Neuberger J. Clinical guidelines on the management of hepatitis C. *Gut* 2001;**49**Suppl 1:1–21.
3. Cramp ME, Rosenberg W. Guidance on the treatment of hepatitis C incorporating the use of pegylated interferons. London: British Society for Gastroenterology; 2003. (URL: http://www.bsg.org.uk/pdf_word_docs/pegylated_2003.doc)
4. EASL International Consensus Conference on Hepatitis C, Paris, 26–28 February 1999, Consensus Statement. European Association for the Study of the Liver. *J Hepatol*. 1999;**30**:956–61.

Resources used to retrieve model parameters

A non-exhaustive list of resources used to retrieve model parameters includes:

- on-line databases, including MEDLINE, PreMEDLINE, EMBASE, The Cochrane Library (including the Cochrane Systematic Review Database, Cochrane Central Register of Controlled Trials), Web of Knowledge, Science Citation Index, ISI Proceedings, DARE, NHS EED, CRD HTA database, Econlit
- clinical Trial Registers in the UK and abroad (Current Controlled Trials, National Research Register, NIH Clinical Trials Database)
- websites of regulatory agencies (e.g. FDA, EMEA and MHRA)
- websites of the Professional Groups such as BASL, EASL and the Advisory Group on Hepatitis (AGH) and any associated databases
- websites of the UK Department of Health and the Health Protection Agency
- websites of manufacturers of health technologies for HCV
- research groups or other groups with special interest in HCV prevention and treatment identified through literature searches and contact with experts
- websites of patients' associations (Hepatitis C Trust, British Liver Trust).

Appendix 3

Recently funded, ongoing and recently completed research in the area of HCV and injecting drug use

Department of Health Policy Research Programme Research on Hepatitis C

Hepatitis C and intravenous drug misuse initiative.

A programme of research was commissioned in 2001 with a budget of £0.5 million. These studies are complete.

1. Comparison of sensitivity and specificity of Epitope Orasure and Sarstedt Salivette oral fluid, and dried blood spot, laboratory tests to detect antibodies to hepatitis C virus among injecting drug users (Ms A Judd, Imperial College School of Medicine).
2. The efficacy of enhanced counselling in the primary prevention of hepatitis C among injecting drug users: a randomised controlled trial (Dr M Abou-Saleh, St George's Hospital Medical School).
3. A study of the impact of HCV screening on injecting risk behaviour reported by injecting drug users (Dr M Walker, PHLS Bangor).
4. A cohort study to assess prevalence and incidence of, and risk factors for, hepatitis C virus infection among new injecting drug users (Professor G Stimson, Imperial College School of Medicine).

Other studies

1. A large UK survey into knowledge and attitudes in IDUs and clinicians has recently been completed.
2. A number of case-finding pilot studies are under way.

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

HTA Commissioning Board

Members

Current and past membership details of all HTA 'committees' are available from the HTA website (www.hta.ac.uk)

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern, Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Ms Norma Armston, Lay Member, Bolton

Professor Max Bachmann Professor of Health Care Interfaces, Department of Health Policy and Practice, University of East Anglia

Professor Rudy Bilous Professor of Clinical Medicine & Consultant Physician, The Academic Centre, South Tees Hospitals NHS Trust

Dr Paul Cockcroft, Consultant Medical Microbiologist and Clinical Director of Pathology, Department of Clinical Microbiology, St Mary's Hospital, Portsmouth

Professor Adrian K Dixon, Professor of Radiology, University Department of Radiology, University of Cambridge Clinical School

Dr David Elliman, Consultant Paediatrician/ Hon. Senior Lecturer, Population Health Unit, Great Ormond St. Hospital, London

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales Swansea

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medicines & Healthcare Products Regulatory Agency, London

Professor William Rosenberg, Professor of Hepatology, Liver Research Group, University of Southampton

Dr Susan Schonfield, Consultant in Public Health, Specialised Services Commissioning North West London, Hillingdon Primary Care Trust

Dr Phil Shackley, Senior Lecturer in Health Economics, School of Population and Health Sciences, University of Newcastle upon Tyne

Dr Margaret Somerville, PMS Public Health Lead, Peninsula Medical School, University of Plymouth

Dr Graham Taylor, Scientific Director & Senior Lecturer, Regional DNA Laboratory, The Leeds Teaching Hospitals

Professor Lindsay Wilson Turnbull, Scientific Director, Centre for MR Investigations & YCR Professor of Radiology, University of Hull

Professor Martin J Whittle, Associate Dean for Education, Head of Department of Obstetrics and Gynaecology, University of Birmingham

Dr Dennis Wright, Consultant Biochemist & Clinical Director, Pathology & The Kennedy Galton Centre, Northwick Park & St Mark's Hospitals, Harrow

Pharmaceuticals Panel

Members

Chair,
Dr John Reynolds, Chair Division A, The John Radcliffe Hospital, Oxford Radcliffe Hospitals NHS Trust

Professor Tony Avery, Head of Division of Primary Care, School of Community Health Services, Division of General Practice, University of Nottingham

Ms Anne Baileff, Consultant Nurse in First Contact Care, Southampton City Primary Care Trust, University of Southampton

Professor Stirling Bryan, Professor of Health Economics, Health Services Management Centre, University of Birmingham

Mr Peter Cardy, Chief Executive, Macmillan Cancer Relief, London

Professor Imti Choonara, Professor in Child Health, Academic Division of Child Health, University of Nottingham

Dr Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Dr Karen A Fitzgerald, Consultant in Pharmaceutical Public Health, National Public Health Service for Wales, Cardiff

Mrs Sharon Hart, Head of DTB Publications, *Drug & Therapeutics Bulletin*, London

Dr Christine Hine, Consultant in Public Health Medicine, South Gloucestershire Primary Care Trust

Professor Stan Kaye, Cancer Research UK Professor of Medical Oncology, Section of Medicine, The Royal Marsden Hospital, Sutton

Ms Barbara Meredith, Lay Member, Epsom

Dr Andrew Prentice, Senior Lecturer and Consultant Obstetrician & Gynaecologist, Department of Obstetrics & Gynaecology, University of Cambridge

Dr Frances Rotblat, CPMP Delegate, Medicines & Healthcare Products Regulatory Agency, London

Professor Jan Scott, Professor of Psychological Treatments, Institute of Psychiatry, University of London

Mrs Katrina Simister, Assistant Director New Medicines, National Prescribing Centre, Liverpool

Dr Richard Tiner, Medical Director, Medical Department, Association of the British Pharmaceutical Industry, London

Dr Helen Williams, Consultant Microbiologist, Norfolk & Norwich University Hospital NHS Trust

Current and past membership details of all HTA 'committees' are available from the HTA website (www.hta.ac.uk)

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell,
Consultant Vascular and General Surgeon, Department of Surgery, Royal Devon & Exeter Hospital

Dr Aileen Clarke,
Reader in Health Services Research, Public Health & Policy Research Unit, Barts & the London School of Medicine & Dentistry, London

Dr Matthew Cooke, Reader in A&E/Department of Health Advisor in A&E, Warwick Emergency Care and Rehabilitation, University of Warwick

Dr Carl E Counsell, Clinical Senior Lecturer in Neurology, Department of Medicine and Therapeutics, University of Aberdeen

Ms Amelia Curwen, Executive Director of Policy, Services and Research, Asthma UK, London

Professor Gene Feder, Professor of Primary Care R&D, Department of General Practice and Primary Care, Barts & the London, Queen Mary's School of Medicine and Dentistry, London

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, Department of General Practice and Primary Care, South Tees Hospital NHS Trust, Middlesbrough

Ms Bec Hanley, Co-Director, TwoCan Associates, Hurstpierpoint

Ms Maryann L Hardy, Lecturer, Division of Radiography, University of Bradford

Professor Alan Horwich, Director of Clinical R&D, Academic Department of Radiology, The Institute of Cancer Research, London

Dr Simon de Lusignan, Senior Lecturer, Primary Care Informatics, Department of Community Health Sciences, St George's Hospital Medical School, London

Professor Neil McIntosh, Edward Clark Professor of Child Life & Health, Department of Child Life & Health, University of Edinburgh

Professor James Neilson, Professor of Obstetrics and Gynaecology, Department of Obstetrics and Gynaecology, University of Liverpool

Dr John C Pounsford, Consultant Physician, Directorate of Medical Services, North Bristol NHS Trust

Karen Roberts, Nurse Consultant, Queen Elizabeth Hospital, Gateshead

Dr Vimal Sharma, Consultant Psychiatrist/Hon. Senior Lecturer, Mental Health Resource Centre, Cheshire and Wirral Partnership NHS Trust, Wallasey

Dr L David Smith, Consultant Cardiologist, Royal Devon & Exeter Hospital

Professor Norman Waugh, Professor of Public Health, Department of Public Health, University of Aberdeen

Expert Advisory Network

Members

Professor Douglas Altman,
Director of CSM & Cancer Research UK Med Stat Gp, Centre for Statistics in Medicine, University of Oxford, Institute of Health Sciences, Headington, Oxford

Professor John Bond,
Director, Centre for Health Services Research, University of Newcastle upon Tyne, School of Population & Health Sciences, Newcastle upon Tyne

Mr Shaun Brogan,
Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE,
Chief Executive, Office of the Chief Executive. Trust Headquarters, Altnagelvin Hospitals Health & Social Services Trust, Altnagelvin Area Hospital, Londonderry

Ms Tracy Bury,
Project Manager, World Confederation for Physical Therapy, London

Professor Iain T Cameron,
Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark,
Medical Writer & Consultant Pharmacist, Rossendale

Professor Collette Clifford,
Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham, Edgbaston, Birmingham

Professor Barry Cookson,
Director, Laboratory of Healthcare Associated Infection, Health Protection Agency, London

Professor Howard Cuckle,
Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Dr Katherine Darton,
Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux,
Professor of Paediatric Epidemiology, London

Mr John Dunning,
Consultant Cardiothoracic Surgeon, Cardiothoracic Surgical Unit, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw,
Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles,
Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby,
Professor of Community Rehabilitation, Institute of General Practice and Primary Care, University of Sheffield

Mr Leonard R Fenwick,
Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Professor David Field,
Professor of Neonatal Medicine, Child Health, The Leicester Royal Infirmary NHS Trust

Mrs Gillian Fletcher,
Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn,
Professor of Medicine, Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham

Ms Grace Gibbs,
Deputy Chief Executive, Director for Nursing, Midwifery & Clinical Support Services, West Middlesex University Hospital, Isleworth

Dr Neville Goodman,
Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Alastair Gray,
Professor of Health Economics, Department of Public Health, University of Oxford

Professor Robert E Hawkins,
CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor Allen Hutchinson,
Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Dr Duncan Keeley,
General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping,
Research Degrees Programme Director & Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy,
Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay,
Professor of Psychiatry for the Elderly, University of Leicester, Leicester General Hospital

Professor Julian Little,
Professor of Human Genome Epidemiology, Department of Epidemiology & Community Medicine, University of Ottawa

Professor Rajan Madhok,
Medical Director & Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor David Mant,
Professor of General Practice, Department of Primary Care, University of Oxford

Professor Alexander Markham,
Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Chris McCall,
General Practitioner, The Hadleigh Practice, Castle Mullen

Professor Alistair McGuire,
Professor of Health Economics, London School of Economics

Dr Peter Moore,
Freelance Science Writer, Ashtead

Dr Sue Moss, Associate Director,
Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Mrs Julietta Patnick,
Director, NHS Cancer Screening Programmes, Sheffield

Professor Tim Peters,
Professor of Primary Care Health Services Research, Academic Unit of Primary Health Care, University of Bristol

Professor Chris Price,
Visiting Chair – Oxford, Clinical Research, Bayer Diagnostics Europe, Cirencester

Professor Peter Sandercock,
Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, Genetics Department, St James's University Hospital, Leeds

Dr Ken Stein,
Senior Clinical Lecturer in Public Health, Director, Peninsula Technology Assessment Group, University of Exeter

Professor Sarah Stewart-Brown,
Professor of Public Health, University of Warwick, Division of Health in the Community Warwick Medical School, LWMS, Coventry

Professor Ala Szczepura,
Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor,
Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster,
Consumer member, HTA – Expert Advisory Network

Current and past membership details of all HTA 'committees' are available from the HTA website (www.hta.ac.uk)

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@hta.ac.uk
http://www.hta.ac.uk

ISSN 1366-5278