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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.

Backloading Method of sharing drugs by injecting drug users (IDUs) involving the use of the same syringe but different needles.

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

Confounding A form of systematic error in an observation where an apparent association (e.g. between treatment and outcome) is artefactual, which is due to the effect of a separate factor that influences outcome.

Cookers Equipment used to heat and dissolve drugs by IDUs.

Cottons Material used to filter particulate matter from solutions of drugs used by IDUs.

Enzyme-linked immunosorbant assay A test used to identify antibodies to hepatitis C virus (HCV).

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

Interferon There are several forms of interferons. Unless otherwise stated, it is used in this report to refer to interferon-α.

Intravenous drug user Drug user who injects by the intravenous route.

Medical Outcomes Survey Quality-of-life questionnaire (a portion of which is the SF-36 quality-of-life questionnaire).

Negative predictive value The proportion of people who have a negative diagnostic test result that do not have the disease.

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

Positive predictive value The proportion of people with a positive diagnostic test result that have the disease.

Quality-adjusted life-year (QALY) A measure of health outcome that weights time spent in a health state according to the quality of that health state (see also utility).

Randomised controlled trial A study that randomly allocates participants to receive competing alternative treatments in order to control for known and unknown confounding effects.

Recombinant immunoblot assay A screening test for HCV.

Rinse water Water used to rinse drug paraphernalia.

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

Sexually transmitted disease Diseases transmitted through sexual intercourse.

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 HCV RNA, which is maintained for at least 24 weeks after treatment stops (< 100 copies/ml).

continued

Glossary *contd*

Time trade-off A technique for deriving utilities of health states. Involves trading a longer period in the health state of interest with a shorter period in perfect health to reveal the subject's preference-based value for the health state of interest.

Utility A measure of the value attached to a health state. Used to weight time spent in that state in cost–utility analyses (e.g. cost per QALY).

Venereal disease Sexually transmitted disease.

Virological response Absence of virus particles in the blood.

Visual analogue scale A technique for deriving utilities of health states, which involves rating a specific health state on a simple linear scale.

List of abbreviations

ALT	alanine transferase
CAH	chronic active hepatitis
CEA	cost-effectiveness analysis
CI	confidence interval
CUA	cost–utility analysis
ELISA	enzyme-linked immunosorbant assay
GP	general practitioner
GUM	genitourinary medicine
HA	health authority
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HRQoL	health-related quality of life
IDU	injecting drug user
IVDU	intravenous drug user
NANBH	non-A or non-B hepatitis
NICE	National Institute for Clinical Excellence
NPV	negative predictive value
NSC	National Screening Committee
NSSAL	National Survey of Sexual Attitudes and Lifestyles
OR	odds ratio
PCR	polymerase chain reaction
PPV	positive predictive value
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RIBA	recombinant immunoblot assay
SD	standard deviation

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

Executive summary

Background

Screening for hepatitis C virus (HCV) infection is the offer of a test in people not complaining of symptoms associated with HCV or requesting a test of HCV status. Screening for HCV is currently undertaken in a range of groups and settings, and supported by several consensus statements internationally and NHS policy with respect to screening in injecting drug users (IDUs). Screening for HCV stands up reasonably well to the UK National Screening Committee criteria, but some important uncertainties remain.

The natural history of HCV is characterised by high rates of chronicity and, after a long but variable latent period, clinically important sequelae. Injecting drug use is the most important route for infection; sexual transmission appears to be less significant. Prevalence of HCV among IDUs is high. This is lower than in some community-based studies in the UK, but reflects the prevalence among those in contact with drug services. Genitourinary medicine (GUM) clinic attenders do not have a markedly higher prevalence of HCV than the general population and the majority of GUM clinic attenders with HCV have a history of injecting drug use.

People with HCV have reduced quality of life (even in mild disease and when adjusting for co-morbidities), which is, for example, similar or worse than patients with non-insulin-dependent diabetes mellitus. Antiviral treatment appears to improve quality of life.

Objectives

To review the clinical effectiveness and cost-effectiveness of screening for HCV in IDUs and GUM clinic attenders in the UK. Further objectives were to determine the extent of screening for HCV in England and whether knowledge of HCV status causes behavioural changes among infected or uninfected people that may reduce the spread of HCV.

Methods

Review of economic evaluations of screening programmes

Electronic databases were searched from 1996 to 2001 using a broad strategy to identify existing evaluations of screening programmes for HCV. Articles were appraised using a standard framework.

Study of current practice in HCV screening (diffusion study)

In October 2001, a questionnaire survey of all GUM clinics, health authorities and prisons, and 50% of drug services in England was conducted. Participants were asked about screening, diagnosis and treatment within their organisation.

Cost-effectiveness model

The model examined the progress of hypothetical cohorts through the stages of screening, diagnosis and treatment in two separate populations: IDUs in contact with drug services and GUM clinic attenders. Screening was compared to a no-screening scenario and cost–utility (£/quality-adjusted life-year (QALY)) was estimated. Literature searches were performed to identify values for the parameters included in the model. Costs were discounted at 6% and benefits at 1.5%. Extensive sensitivity analyses and some multi-way analyses were conducted.

Effect of knowledge on risk behaviour

Electronic databases were searched from 1981 to 2002 for studies on behavioural changes associated with gaining knowledge of HCV status. Further relevant studies were sought through citation searching, scrutiny of the references obtained and from experts.

Results

Review of economic evaluations of screening programmes

Six relevant studies of screening strategies (one cost–utility analysis, one cost–benefit analysis and four cost-effectiveness analyses) were revealed. Only one study addressed screening in the UK. All of the other studies were of limited scope

and/or relevance to the UK setting. The UK report estimated the cost–utility of screening as £10,177/QALY in IDUs and £27,125/QALY in GUM clinic attenders. Sensitivity analyses showed a range of possible cost–utilities: £12,580–194,026/QALY in GUM clinic attenders and £3333–81,438/QALY in IDUs. Significant methodological weaknesses were recognised by the authors.

Study of current practice in HCV screening (diffusion study)

The response rate was 65% overall, and 26% of drug services reported screening compared to 92% of GUM clinics. The survey revealed that a wide range of eligibility criteria for screening are used, with many organisations screening only those considered to be at increased risk of infection. A range of screening tests are reported, although enzyme-linked immunosorbant assay followed by polymerase chain reaction is the commonest combination. Organisations that conduct screening are often not closely associated with those that consider treatment, and this may mean that people are screened who would not be considered for treatment. Alternative reasons for screening under these circumstances are unknown. Health authorities may not be fully aware of the extent of screening locally, which may suggest a lack of strategic overview of screening and that the implications of initiating screening may not have been considered across healthcare communities. Treatment for HCV is widely, although not universally, available. Use of pegylated interferon in combination therapy appears at the time of writing limited.

Cost-effectiveness model

Screening for HCV in IDUs was estimated to yield benefits over no screening at a cost of £28,120/QALY. This estimate was reasonably stable in a wide range of one-way sensitivity analyses. Lower cost-effectiveness may be associated with low acceptance of liver biopsy and/or acceptance of treatment with combination therapy. Pegylated interferon (although not exhaustively reviewed) may substantially increase the cost-effectiveness of screening. The cost-effectiveness of universal screening in GUM clinics was estimated to be £84,570/QALY and was subject to considerable uncertainty. Selective screening in GUM clinics is likely to be more cost-effective than universal screening. However, only under assumptions of high acceptance of screening and/or adherence to treatment do selective screening strategies in GUM clinics achieve levels of cost-effectiveness that might be considered to represent good value for money, in the absence of other considerations, by policy makers.

Effect of knowledge on risk behaviour

Four relevant studies were identified (three cross-sectional and one longitudinal) and all had considerable methodological limitations. There was no compelling evidence to support the idea that behavioural changes would occur as a result of learning HCV status, either among those shown to be HCV positive (who may be encouraged to reduce the risk of infecting others) or those shown to be HCV negative (who might consider protecting themselves from infection), although the evidence base was insufficient to reject the possibility that such effects exist.

Conclusions

The objectives of screening for HCV should be clarified. Policy makers might wish to elucidate whether the primary purpose of screening is to: identify infected individuals for treatment, enable monitoring of infected individuals regardless of eligibility for treatment, achieve harm reduction in relation to the progression of HCV disease through reducing alcohol consumption or influence behaviour in relation to the spread of HCV. Evidence in support of objectives other than the treatment of infected individuals appears to be limited.

Screening for HCV in IDUs in contact with services is moderately cost-effective (about £30,000/QALY) and reasonably stable when explored in extensive one-way sensitivity analyses. Uncertainty around acceptability of screening and adherence to treatment and the simple nature of our model leads us to recommend caution in accepting this estimate.

Universal screening in GUM clinics is less cost-effective and subject to greater uncertainty than screening IDUs in contact with services. Assessment of selective screening policies in the GUM clinic setting is restrained by scarcity of information on the epidemiology of HCV in groups other than IDUs. While selective screening may be more cost-effective and affordable than universal screening, we believe that it remains open to question whether seeking people other than IDUs for screening represents a cost-effective use of NHS resources.

Research recommendations

Further research in the following areas would be valuable.

- The epidemiology and long-term natural history of HCV in different populations, particularly those presenting to GUM clinics.

- A systematic review of the role of sexual transmission of HCV.
- Improved modelling for the cost-effectiveness of screening based on more sophisticated methods, for example, discrete event simulation to introduce a more stochastic approach, extending the analysis beyond the prevalent round of screening and incorporating more realistic modelling of the no-screening alternative.
- Further empirical investigation into screening in different settings, including more detailed investigation of screening in GUM clinics, in particular to provide more data on acceptance and adherence within screening programmes and reasons for selection of eligibility criteria for screening.
- Development and evaluation of interventions to produce behavioural changes among IDUs in relation to HCV infection. Studies should be longitudinal, specify the intervention more clearly and measure behaviour changes more precisely and with greater power to demonstrate effects. This should include an evaluation of the information currently given to participants in screening programmes.
- Research to consider whether there are differences in effect according to specific characteristics of the population and setting for intervention, such as duration of injecting, presence of co-infection or morbidity, sex or setting in which screening is conducted.
- Monitoring of treatment response and long-term follow-up of people identified through screening.

Chapter 1

Aim and background

Research questions

Research questions and overview

The aim of this technology assessment was to answer the question:

- what is the effectiveness and cost-effectiveness of screening for hepatitis C virus (HCV) in injecting drug users (IDUs) and genitourinary medicine (GUM) clinic attenders in the UK?

Two other questions of relevance to policy were also considered:

- how much screening for HCV is currently carried out in England?
- does knowing HCV status produce a change in behaviour, in both infected and uninfected people, that may reduce the risk of HCV spread?

Screening was taken to mean the offer of a test of HCV status to people who are not seeking such a test and who are not seeking help for symptoms that may be associated with HCV infection. For the purposes of the evaluation of screening, it is important to include subsequent diagnostic procedures and treatment for those found to be infected and eligible for treatment. These elements together constitute a screening programme.

The approach to screening considered in this assessment was targeted screening – of a specified group (IDUs) in a range of settings and of all people in contact with a particular open-access clinical service (GUM clinics) – rather than a whole population approach to screening. The establishment of a screening programme in the sense that it exists for the detection of early cases of breast cancer and the systematic and periodic offer of testing within that group was not considered. This assessment did not consider transfusion-acquired infection and the value of "look back" exercises to identify people infected before the HCV agent was identified, nor did it consider antenatal screening to prevent maternal–child infection (vertical transmission).

Screening seeks out asymptomatic individuals in order to identify disease or significant risk factors for disease. The fact that recipients of screening are not aware of their status or actively seeking help means that a large number of people will be drawn into health services and may suffer harm, for example, the anxiety or false reassurance resulting from misclassification by screening tests. This places an ethical responsibility on those conducting screening to consider the balance of benefits and harms.

There are four reasons for screening for infectious disease.

- To identify individuals who might be effectively treated.
- To inform people of their status (that is, infected or not) on the assumptions that (a) such knowledge has intrinsic value and (b) that knowing whether they are infected or not may cause people to change their behaviour in order to reduce the spread of the disease. People who are infected may reduce the risk of infecting others and those who are not infected may take greater precautions to protect themselves against infection.
- To allow monitoring of people with HCV who are currently ineligible for treatment but who many become eligible in the future.
- To promote harm reduction to individuals to slow progression of HCV.

The assessment included several elements that were relevant to the research question (for more details, see methods chapter). Firstly, as background, the current consensus for screening was reviewed and screening against the main criteria promoted for the evaluation of screening programmes was considered briefly.

The rest of the report details the methods and results of four main activities carried out to address the aims.

- A review of existing evaluations of screening programmes. This was necessary to ensure that the research question had not been adequately addressed by existing work.
- A review of the effects on behaviour of knowledge of HCV status. Current evidence of whether gaining knowledge of HCV status is likely to produce such changes in behaviour

was examined, because this may be considered a reason for screening independent of the effectiveness of treating established infection in individuals.
- A survey of current screening practice. This provided some estimates that were required by the model of screening (see below) and described the extent of provision of screening (diffusion of the technology) in England in 2001. It, therefore, provided relevant information for policy makers considering the value of screening and potential responses to the central element of the assessment – the modelling study.
- A model of screening in the relevant populations. A simple model examining a prevalent round of screening was developed (i.e. re-screening at intervals was not considered). A modelling approach to screening, even a relatively simple approach such as taken here, allows relevant data on a wide range of aspects of the programme to be brought together, for example, size of the eligible pool of participants, effectiveness and cost of the screening test, effectiveness and cost of treatment and follow-up and likely adherence of participants to the process of screening from initial identification through to successful treatment. The model gave an estimate of the cost–utility of screening, measured in cost per quality-adjusted life-year (QALY).

Debate and consensus regarding screening for HCV

HCV is a predominantly blood-borne infection. Screening for HCV has been suggested for populations at risk of infection through this route. Since the introduction of serological screening of blood donations, IDUs have become the most important at-risk group for HCV infection, although others have been suggested for targeted screening, as described later. Hitherto, there has not been a clear picture of the prevalence of screening programmes for HCV in the UK. However, screening is undertaken in a range of settings including drug treatment services,[1] GUM clinics[2] and prisons.[3] Antenatal screening has recently been investigated.[4]

The reasons for different positions on HCV screening can be summarised as follows.[5,6]

The case favouring screening is that:

- HCV is a major public health problem
- effective treatment is available
- effective and safe screening and diagnostic tests are available
- long-term uncertainties about treatment can be addressed through screening
- increased awareness may promote prevention of onward transmission of infection
- increased awareness may promote and/or accelerate towards cessation of injecting drug use with slowed progression of HCV through reduced alcohol consumption.

The case against screening is that:

- the clinical course of HCV is uncertain and thus the impact of treatment is insufficiently certain to commence screening
- biopsy carries some risk and this must be more carefully balanced in the decision to screen
- psychological morbidity from screening should also be considered
- effectiveness of treatment is limited
- long-term effectiveness of treatment remains uncertain
- increased awareness of serological status may not limit the spread of infection
- the impact of screening on the health service would be considerable and would call for a considerable increase in capacity before commencing with such a programme
- increased awareness of HCV may not result in cessation of injecting drug use and reduced alcohol consumption.

A range of professional organisations and expert groups have reached slightly different positions of consensus of screening for HCV, mostly in the USA. These are summarised in *Table 1*.[7–11]

There is a reasonable congruence between these position statements. The groups most frequently identified are blood product recipients and intravenous drug users (IVDUs). Consensus is less well developed regarding screening in GUM clinics. The question of whether this is simply a setting in which to identify IDUs or whether there is a separate case for screening based on risks associated with sexual transmission is currently unresolved. The evidence for sexual transmission and prevalence in GUM clinics is reviewed later in this assessment.

The methods by which consensus was reached by the groups shown in *Table 1* has not been detailed in most cases and the evidence supporting their positions not systematically reviewed. Professionals, understandably, dominated the consensus conferences. Indeed, it is unclear

TABLE 1 *Consensus statements on screening for HCV*

Consensus group	Date of consensus	Populations approved for HCV screening
European Association for the Study of the Liver[7]	1999	• Recipients of blood products before 1991 • Haemophiliacs • People on haemodialysis • Infants of mothers who are HCV positive • Current or previous IVDUs • Organ donors
Centers for Disease Control[8]	1998	• IVDUs • Blood product recipients
American Academy of Pediatricians[9]	1998	• IVDUs • People on haemodialysis • Infants at > 5% risk of infection • Recipients of two immunoglobulin products between 1993 and 1994
France – range of professional and lay people[10]	1997	• IVDUs • Blood product recipients before 1991 • People on haemodialysis • Prisoners • "Certain subgroups of medical personnel, e.g. haemodialysis nurses"
National Institutes for Health[11]	1997	• Infants and partners of people infected with HCV • High-risk groups, e.g. IVDUs and blood product recipients

what role, if any, public preference played in informing the views of most consensus development approaches. An interesting exception to this was the French consensus statement, which involved a wide range of stakeholders.

The Advisory Council on the Misuse of Drugs is a body constituted under the Misuse of Drugs Act 1971 that advises the UK government. In a report published in 2000, the Council recommended the following.[12]

- The expansion of opportunities for voluntary HIV/HCV/hepatitis B virus (HBV) testing accessible and appropriate to clients' needs and accompanied by counselling and support from adequately trained staff.
- A more proactive approach should be taken to testing in areas of known or suspected high prevalence, targeting the provision of testing at people who engage in high-risk behaviours.
- Agencies should ensure that screening for virus infection is routinely and appropriately used, with pre- and post-test counselling on the implications of the results.

In its response,[13] the Department of Health cited UK guidelines for the management of drug misuse and dependence,[14] which state that drug users who are or have been at risk of contracting HCV should be offered well-informed advice and should be made aware of the implications of a positive test. While these recommendations constitute a policy in favour of screening for HCV for IDUs, some issues are unclear. How far should opportunities for voluntary testing be expanded and will there be a trade-off between equity and efficiency (e.g. would voluntary testing be taken up by those who stand to benefit directly from screening)? The levels at which prevalence should be defined as high are unclear and agencies that should consider routine screening (the meaning of which is not defined) are not specified.

No specific policy on screening of people who have never been IDUs in GUM clinics was found, although the Advisory Council's recommendations may have been influential in establishing screening in this setting for IDUs and people with no history of drug misuse.

Some commentators have expressed concerns that any policy of limiting the availability of screening and treatment for HCV would be inequitable and may reflect stigma and social unpopularity associated with particular populations rather than clinical need. Equity considerations regarding screening were beyond

the scope of this assessment, but, we believe, should be considered in open debate, taking into account issues of affordability, efficiency (which this assessment considers) and the wider concerns about the treatment of particular populations expressed by Best and colleagues.[15]

Since the publication of WHO criteria for evaluating screening programmes in the 1960s,[16] the need to satisfy separate criteria has been the predominant approach to deciding about the value of screening programmes. The UK National Screening Committee (NSC) has an extended set of criteria used to evaluate potential screening programmes.[17] It is NHS policy that all screening programmes should be considered by the NSC before implementation.

HCV screening – performance against evaluation criteria

Criteria-based screening programme evaluation is a useful, although still imperfect, method for taking decisions about screening. Modelling of existing data has some advantages, in particular, the ability to integrate estimates for the different elements of screening and treatment programmes and to explore uncertainty systematically. It is often constrained by the availability and quality of evidence. Randomised controlled trials (RCTs) are considered the gold standard for evaluating the effectiveness of screening programmes, although they are complex and expensive to perform. There have been no RCTs of HCV screening. The long course of disease is an important constraint on conducting trials.

The rest of this section gives a brief overview of HCV screening set against the UK NSC criteria.[17]

1. The condition should be an important health problem

HCV is clearly an important public health problem, affecting up to 1% of the general population and approaching 90% among some groups of IDUs. Chronicity is common, and the sequelae of chronic infection contribute significantly to the global burden of disease. The epidemiology of HCV is described in more detail later in the chapter.

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, or disease marker, and a latent period or early asymptomatic stage

The natural history of HCV is moderately well understood. Although the causative agent was identified relatively recently, there is extensive information on the natural history of non-A or non-B hepatitis (NANBH), the majority of cases of which are thought to be due to HCV. The criterion requires our understanding of natural history to be sufficient to be sure that the asymptomatic stage precedes significant disease. This is clearly met for HCV. However, what is less clear is whether the natural course of disease is significantly different in IDUs. This is less important for considering whether the criterion is met or not as for considering the likely burden of disease that will be prevented by screening and treatment.

There is clearly a long latent period between infection and cirrhosis. Poynard and colleagues estimate a median of 30 years,[18] although the course is variable. In one-third of this historical cohort, cirrhosis had developed within 20 years and in one-third the clinical course was clearly very slow, possibly meaning that cirrhosis would be unlikely even 50 years after infection.[18] This suggests that screening of infected individuals early in the course of disease may, in some cases, represent unnecessary over-treatment, although it remains currently impossible to predict outcome on an individual basis as a means of improving the efficiency of screening.

3. All cost-effective primary prevention interventions should have been implemented as far as practicable

Primary prevention efforts to control the spread of HCV fall into two main groups – ensuring that blood products are free of viral contamination and preventing spread through behavioural change among IDUs. The second group includes efforts through health education to delay or prevent the onset of injecting, needle exchange programmes and other harm reduction strategies. Reducing vertical and sexual transmission should also be considered, although they are less important than parenteral infection. This assessment includes a systematic review of the evidence on whether acquiring knowledge of HCV infection status results in changes in behaviours related to the spread of HCV to inform this important consideration independently of the cost-effectiveness of screening and treatment of eligible individuals (see the Impact of knowledge of HCV status on behaviour section in the results chapter). It is beyond the scope of the assessment to consider whether current investments in primary prevention efforts are implemented as far as practicable. Others have argued that there is scope to increase primary prevention.[19]

4. There should be a simple, safe, precise and validated screening test. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed. The test should be acceptable to the population and there should be agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

As described in the Screening test performance section of the results chapter, diagnostic tests for HCV are highly sensitive and specific. However, as with any test, misclassification remains a reality. Liver biopsy is required to stage infection as part of the work-up towards treatment and there are clear criteria for treatment based on the degree of chronic active hepatitis (CAH) and informed by the results of trials of combination therapy. Treatment of mild hepatitis and cirrhosis is currently contentious. Acceptability of screening tests and subsequent liver biopsy is less clear, particularly among IDUs. Biopsy is not without risks to the patient and potential for misclassification. These issues have been addressed within this assessment as part of the modelling of the cost-effectiveness of screening.

5. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment. There should be agreed evidence-based policies covering who should be offered treatment and the appropriate treatment to be offered. Clinical management of the condition and patient outcomes should be optimised by all healthcare providers prior to participation in screening

The National Institute for Clinical Excellence (NICE) has accepted the value of combination therapy for HCV within the NHS for people with moderate CAH.[20] However, does early treatment of cases identified through screening confer advantages? This is probably clearer for HCV than for other conditions, such as prostate or cervical cancer where the effectiveness of treatment options in early disease are far from certain. Where HCV cases would have progressed beyond the indications for therapy the argument for early treatment is strong, although the risk of re-infection, particularly among IDUs, remains an unpredictable factor.

The clinical trials of combination therapy had explicit entry criteria defining the extent of our scientific understanding of the effectiveness of treatment, but two concerns can be raised. Firstly, there is already variation in the application of criteria for treatment, as demonstrated in a recent survey of hepatologists,[21] so the existence and application of evidence on who should be offered treatment may not concur. Secondly, selection for treatment should be informed by an understanding of ability to benefit. This, in turn, rests on our understanding of the epidemiology and natural course of infection, which is less clear for IDUs than others given the prevalence of co-infection, re-infection and other health problems independently associated with long-term drug use. In addition, in time, the prevalence pool will contain proportionately more people from this population.

Optimising the clinical management of HCV is a particular problem in developing screening programmes of acceptable quality. While there is uncertainty about the consistency of clinical management of HCV, it may not be wise to introduce screening. On the other hand, it might be argued that the screening programme creates the context for the optimisation of clinical management, as has been seen in the main cancer screening programmes where quality assurance systems are highly developed and systematically applied.

The debate demonstrates that clinical acceptability of screening varies. The social acceptability of screening for HCV is not at all clear. Would the public prefer to see limited and scarce NHS resources spent on *in vitro* fertilisation or HCV screening? Should we direct resources from the development of neonatal intensive care to screening IDUs? There is a clear socio-political dimension to these questions, which deserves airing. These issues are beyond the scope of this assessment but represent important additional considerations in making policy in this area.

Although the economics of treatment for HCV are becoming clearer, it does not follow that screening will represent similarly good value for money to the NHS. This is the focus of the cost-effectiveness modelling undertaken in this assessment.

6. There must be evidence from high-quality RCTs that the screening programme is effective in reducing mortality or morbidity. The information that is provided by the test must be clearly understood by the individual being screened

There are no RCTs of screening for HCV. There is some evidence that information on HCV status is not well understood by IDUs.[22]

7. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public

The debate regarding screening for HCV indicates that complete acceptability may not have been reached, although it could be argued that this is an ideal that is seldom achieved in making healthcare policy. Whether screening for HCV is seen as a healthcare priority by the public is not known.

8. The benefit of the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment). The opportunity cost of the screening programme (including testing, diagnosis, treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money)

The balance of benefits and physical harms and cost-effectiveness are addressed in the modelling study carried out as part of this assessment. Psychological harms arising from anxiety associated with misclassification as false-positives, or associated with side-effects of treatment are not explicitly considered.

9. There must be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards

There is no clear plan for managing and monitoring HCV screening in England and no agreed quality assurance standards. Variation in screening is described in the study of current practice included in this assessment.

10. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

The issue of management infrastructure for HCV screening is a crucial one on which there is little information. The study of current practice reported later in this assessment demonstrated that there is limited strategic programme management of HCV screening in England.

11. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services) to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available

Treatment for HCV has become available only relatively recently. Pegylated interferons represent a possible alternative and a preliminary assessment of conducting treatment using these new agents in the context of a screening programme is included in the cost-effectiveness analysis (CEA).

12. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice

Few detailed data are available on what information is given to people at the time of screening. The survey carried out for this assessment addressed how much time is involved in counselling prior to screening. Limited information on the content of information given to people prior to screening was also collected.

13. Public pressure for widening the eligibility criteria, for reducing the screening interval and for increasing the sensitivity of the testing process should be anticipated. Decisions about these parameters should be scientifically justifiable to the public

There has been very little public debate about screening for HCV, which is currently restricted to target groups and defined settings rather than the whole population. Screening interval is a challenging issue in the context of HCV. Screening tests are highly sensitive relative to those used in other screening programmes.

On the face of it, screening for HCV stands up reasonably well to these criteria but some important uncertainties remain. This assessment is focused mainly on the issue of the effectiveness and cost-effectiveness of a screening programme. By examining the evidence for behavioural change following knowledge of HCV status, the assessment provides useful information for those involved in primary prevention. Furthermore, some light is thrown on some of the organisational issues that are involved in policy-making regarding screening by the survey of current screening.

The next section gives an overview of the natural history and epidemiology of HCV, concentrating on those areas that are of relevance to the modelling study presented later in the assessment, and outlines the impact of HCV on quality of life (QoL).

HCV

Natural history

HCV is a virus of the Flaviviridae family and was first identified in 1989. HCV probably accounted

for about 90% of cases of what was known as NANBH before HCV was identified. Six distinct viral genotypes have since been identified, the most common worldwide being types 1a and 3a.[23] More than 30 subtypes have been identified.

Natural history studies have been difficult to complete for HCV. Onset of infection is rarely recognised and the chronic course is often asymptomatic. Building on the review of natural history studies by Seeff,[24] the following is an outline of the natural history of HCV.

- After infection, HCV RNA can be detected in 1–3 weeks. The acute phase lasts 2–3 months and, although more than 70% of cases experience no symptoms, mild fatigue and jaundice may occur. Virtually all cases show evidence of liver cell injury, as demonstrated by elevated liver enzyme levels. Fulminant liver failure during the acute phase of HCV infection appears to be rare.[25]
- Of people who are infected, 65–85% will develop chronic hepatitis, that is, the virus is not cleared by host immune mechanisms (see *Figure 1*). This strikingly high rate of chronicity may be related to genetic variability among subtypes of HCV.
- Of infected individuals, 20% may progress to development of hepatic fibrosis and cirrhosis, which, in some people, will cause liver failure. Of those that develop cirrhosis, perhaps 20% will develop hepatocellular carcinoma (HCC; see *Figure 1*),[26] although there is considerable variation in estimates of progression rates from HCV-related cirrhosis to HCC.[27]

Factors that influence disease progression include co-infection with HIV or HBV, male gender, older age at infection and alcohol intake. There may be differences in natural history in different populations, depending on mode of infection. There is some evidence that cirrhosis, while being dependent on disease duration, may be more frequent in blood transfusion recipients than IDUs. This finding may be due to smaller average inoculum dose among IDUs.[28] Distribution of genotype may also influence natural progression in different populations. Subtype 1a is more commonly associated with IDUs than blood transfusion recipients and may follow a less severe course.[29] Against these suggestions of slower and milder natural history among IDUs are the uncertain long-term effects of risk of liver disease from drug effects (including alcohol) and co-morbidity.

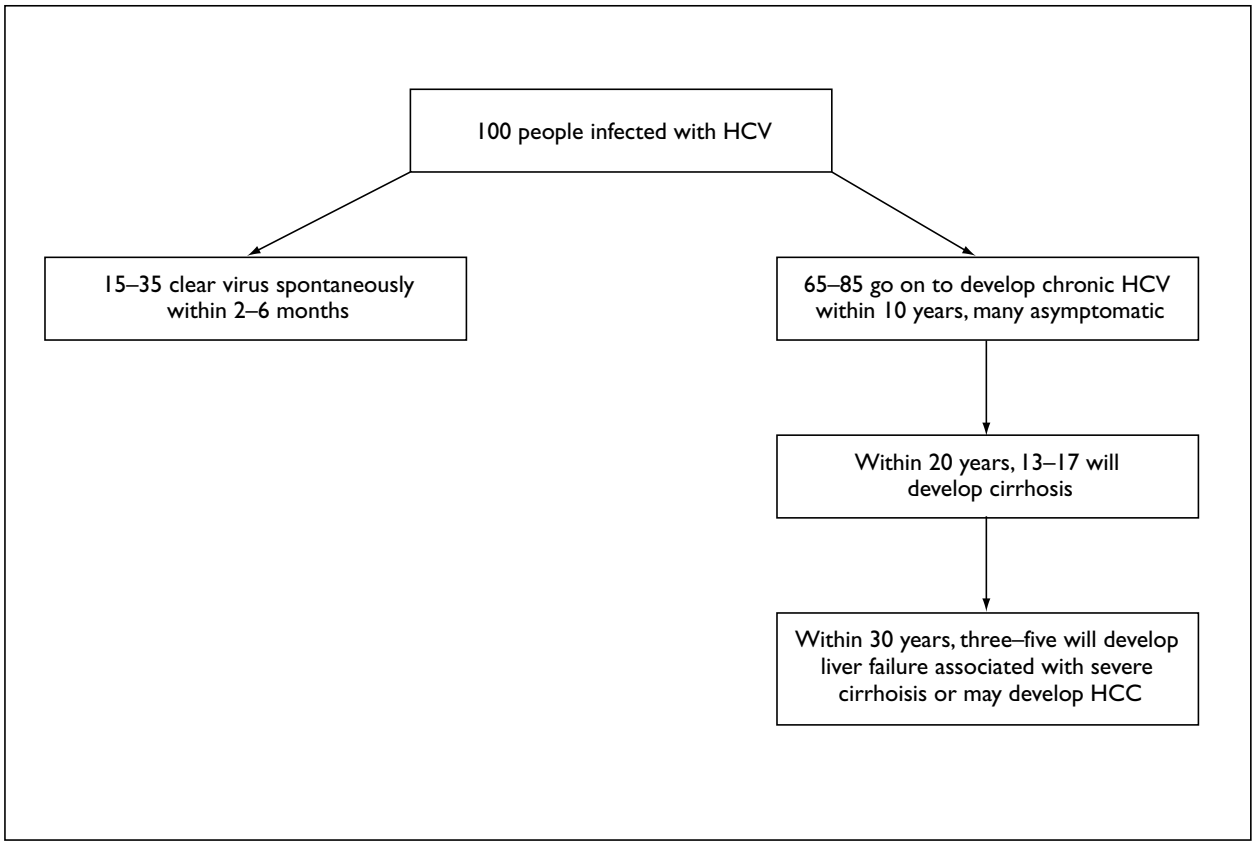

FIGURE 1 *Example of the natural progression of 100 people infected with HCV*

Epidemiology of HCV in the UK

This section outlines the prevalence of HCV in the community in general and low-risk populations in the UK and describes the prevalence of HCV in GUM clinic attenders and IDUs, the populations of interest in this assessment. The importance of sexual transmission of HCV is also discussed.

HCV in the general population

The prevalence of HCV in the USA is estimated at about 1.8% with higher prevalence in males and older people.[30] An estimate of prevalence in unselected populations in the UK suggested a lower prevalence of 0.7% in 1996. This conclusion was based on analysis of residual serum specimens from adults submitted to UK laboratories and is currently unpublished. It has been estimated that there are 200,000–400,000 people living with HCV in the UK.[31]

Routine surveillance of HCV infection by the Public Health Laboratory Service in England shows an increase in the number of confirmed laboratory reports since 1992. Provisional figures for the year 2000 identified 5108 laboratory reports of HCV with the majority being in those aged 24–34 (36%) and 35–44 (27%). Almost two-thirds of reports were in males.

Table 2 shows estimates for anti-HCV prevalence in women attending antenatal clinics, ranging from 0.14–0.80%.[4,32–34] Prevalence appears to be lower in the UK than in other European countries (e.g. 1.55% in France and about 1.0% in Germany[31]). Studies in this group are likely to under-estimate the population prevalence, as men are excluded (in whom HCV is more prevalent) and age range of women using the service is limited. Likelihood of infection increases with duration of injecting drug use and, therefore, age.[35]

Among blood donors, prevalence is lower and ranges from 0.04 to 0.06% (*Table 3*).[36–38] Blood donors are likely to be at lower risk of blood-borne virus infections than the general population (healthy volunteer effect).

HCV in IDUs

Injecting drug use is the most significant risk factor for transmission of HCV in England and Wales and has increased in importance as a source of new infection since the reduction of risk of iatrogenic infection through transfusion of infected blood products since the late 1980s. The importance of injecting drug use as a risk factor has been confirmed in a range of studies, including sero-prevalence studies (see below), routine surveillance and in studies of HCV-positive blood donors.[31]

TABLE 2 *Anti-HCV prevalence in women attending antenatal clinics in the UK*

Study	Study period	Population	Number	Anti-HCV prevalence
Goldberg *et al.*, 2001[32]	1997	Antenatal clinic attenders and women undergoing termination of pregnancy, Dundee	3548	0.6%
Boxall *et al.*, 1994[33]	1990/1991	Women attending antenatal clinics, Birmingham	3522	0.14%
Ward *et al.*, 2000[4]	1997/1998	Antenatal clinic attenders, London	4825	0.8%
Balogun *et al.*, 2000[34]	1996	Serum archive of women attending antenatal clinics in greater London and the northern and Yorkshire region	42,613	London: 0.43% Northern and Yorkshire region: 0.21%

TABLE 3 *Prevalence of anti-HCV among UK blood donors*

Study	Study period	Population	Number	Anti-HCV* prevalence
Mohsen *et al.*, 2001[36]	1991–1998	Five centres in the Trent region	5.3 million	0.05%
McLindon *et al.*, 1995[37]	1991–1993	Northwest England	224,700	0.04%
Public Health Laboratory Service, 1998[38]	1997	England and Wales	280,000	0.06%

* *Anti-HCV antibodies indicate current or past infection*

Prevalence of HCV in IDUs
A recent review of prevalence studies in IDUs included 19 studies across many countries and settings.[39] A uniformly high prevalence of people positive for antibodies against HCV (i.e. people who have been infected, in whom the majority will continue to harbour viruses) was shown, ranging from 59 to 98%. None of the 19 studies were from the UK.

A community-based study of 1949 IDUs in Scotland recruited between 1990–1996 reported a HCV prevalence of 72%.[40] A lower prevalence of 49% was reported in a cross-sectional study of 1864 IDUs in Scottish prisons in the early 1990s.[41]

In England and Wales, an anonymous unlinked testing programme based on salivary testing was introduced in 1998 among IDUs attending specialist drug treatment needle exchange centres.[42] Using voluntary collection of saliva, the survey measures current and prior infection with HBV and HCV across 14 centres in London and 37 centres elsewhere in the UK. The survey has limitations, but probably represents the most up-to-date and comprehensive data on potential candidates for HCV screening in England. Estimates may be lower than the actual number of cases because testing is voluntary. However, as the unit of analysis in the survey is samples and not people, participants may be tested more than once, which will bias estimates for population prevalence upwards. Of the 3731 samples from IDUs tested in 1998, 32% were anti-HCV.[41] Prevalence of HCV varied by region with the highest in London and the northwest. A breakdown by age and gender is shown in *Table 4*.

TABLE 4 *HCV prevalence in IDUs in 1998*

Age		London	Outside London	Total
Male	< 25	25%	9%	11%
	25–34	34%	30%	31%
	≥ 35	62%	50%	54%
	Total	45%	29%	32%
Female	< 25	23%	12%	14%
	25–34	39%	33%	33%
	≥ 35	67%	51%	57%
	Total	44%	29%	32%
Persons	< 25	24%	10%	12%
	25–34	35%	30%	31%
	≥ 35	63%	51%	55%
	Total	45%	29%	32%

Duration of injecting is an important factor determining the incidence of HCV infection. Risk increases with time since first injection. A study of IDUs in Glasgow found that the prevalence of anti-HCV in adult male IDUs rose from 18% in those who were within 5 years of their first injection to 47% in those who first injected 16 or more years ago.[43] A survey of IDUs in 1999 found 10% infected within 2 years, 20% within 5 years, 35% within 8 years and 38% by 11 years.[35]

Prevalence of IDUs in England
Several data sources are available, although each has limitations.[44] The Home Office Drug Addicts Register[45] and NHS Drug Misuse Statistics[46] can only be considered as minimum estimates of community prevalence. Community-based surveys, such as The National Survey of Sexual Attitudes and Lifestyles (NSSAL)[47] and the Drug Usage and Drug Prevention Survey,[48] have reported much higher estimates of drug misuse.

The focus of this assessment is on screening in people presenting to services. In the cost-effectiveness model reported later in this assessment, estimates for the number of people in contact with drug services were required. Since treatment is not available for those who are currently injecting, screening eligibility in the model was restricted to those who have been but are not currently IDUs.

The Drug Misuse Statistics[46] give an estimate of 118,500 people in contact with drug services each year. Of these, 85% are likely to have injected at some time[1] and 60% are likely to be current injectors.[1]

HCV in GUM clinic attenders

This section considers the role of sexual transmission of HCV as well as prevalence of HCV in GUM clinics. This is relevant because knowledge and beliefs about the role of sexual transmission of HCV will determine policies on eligibility for screening within GUM services, depending on whether sexual transmission is considered to be important or whether any increased prevalence in this setting is due to confounding by higher attendance by IDUs. In other words, there are two approaches to screening in GUM clinics that will result in markedly different eligibility strategies.

(a) It might be assumed that HCV is readily transmitted sexually, and, therefore, people seeking help for symptomatic sexually transmitted infec-

tions are likely to have a higher prevalence of HCV infection. Thus, screening could be offered to all attenders or on the basis of sexual behaviours that are considered to carry higher risk of infection.

(b) IDUs are more likely to attend GUM clinics than the general population, based particularly on the interaction between drug use, prostitution and risk of sexually transmitted diseases. In other words, GUM clinics are a setting in which a screening programme could reach the main eligible population and screening should be offered only to people who admit to a previous history of being an IDU.

Sexual transmission

The role of sexual transmission of HCV has been much debated. Genomic studies demonstrate that HCV can be transmitted sexually. Many studies have investigated HCV prevalence in sexual partners of people with HCV, but produced conflicting results with estimates ranging from 0 to 14%.[49] The small size of some studies has limited the precision of findings and there is evidence of the importance of confounding by risk factors for parenteral transmission.

A case–control study in blood donors in the Trent region showed that number of sexual partners and homosexuality were not significant risk factors for infection.[50] There was also evidence of a strong confounding effect of injecting drug use in this study, which was addressed by appropriate multivariate analysis. In a cross-sectional study of risk factors in heterosexual couples in San Francisco, Osmond and colleagues found no association between sexual behaviours within couples or number of sexual partners.[49]

In a seroprevalence study based in a GUM outpatient clinic in central London, Tedder and colleagues tested 1046 samples for HCV and investigated associations with sexual orientation and practices.[51] The results suggested an important role for sexual transmission, particularly among homosexual men (odds ratio (OR) = 7.14). However, this study used first generation enzyme-linked immunosorbant assay (ELISA) testing, which is less sensitive and specific than tests now available. More importantly, the study failed to control adequately for injecting drug use. In contrast, a 1990 study of 129 patients in GUM clinics in San Francisco found that "while having multiple sexual partners in the previous three months, being homosexual or bisexual, engaging in receptive anal intercourse were associated with being positive for antibodies to hepatitis B, these behaviours were not associated with anti-HCV positivity".[52]

Co-infection with other sexually transmitted diseases, especially HIV, may increase risk of infection with HCV and accelerate HCV disease progression.[53] The role of sexual transmission in HCV remains unclear but the prevailing view appears to be that "HCV can be acquired through sexual intercourse, but for most people the probability of this occurring is extremely low".[54] As sexual transmission appears to be less effective for HCV than other agents, notably HBV, intensity of exposure (the number of contacts with infected people) may be a more important determinant of infection risk than overall number of sexual partners, unless a very high proportion of sexual partners are HCV positive.[55]

Number of GUM clinic attenders in England

Information on the number of new cases seen at GUM clinics in England is published annually. In order to preserve confidentiality, all data are anonymised and, therefore, only the number of contacts between service users and professionals is available. The numbers in *Table 5* are, therefore, an over-estimate of the number of people who used GUM services in 1998. Between 1997 and 1998, the total uptake of diagnostic and other GUM services rose by 7% to exceed 1 million.[43,56]

TABLE 5 *Contacts with GUM services in England in 1998*

New diagnoses	507,655
GUM clinic workload	523,835
Total contacts	1,031,490

The NASSL[47] estimated that 0.9% of men and 0.8% of women have contacted a GUM clinic in the last year. Applying this figure to population estimates for England in 1999[57] gives an estimate of 246,636 people per year in contact with GUM services. This estimate was used in the base case of the cost-effectiveness model developed for this assessment.

Prevalence of HCV in GUM clinic attenders

Several studies have been carried out in populations of GUM clinic attendees to estimate both the importance of sexual transmission for HCV and the presence or absence of other risk factors. The prevalence of anti-HCV in four studies is shown in *Table 6*,[51,52,54,58] ranging from 1.5% in Glasgow[54] to 7.7% in San Francisco.[52] All studies have a higher prevalence than blood donor and antenatal clinic populations, although

TABLE 6 *Prevalence of anti-HCV among GUM clinic attenders*

Study	Year	Population	Number	Test	Prevalence
Weinstock *et al.*[52]	1993	San Francisco, USA	1292	ELISA and positive neutralisation	Anti-HCV 7.7%
Goldberg *et al.*, 2001[54]	1996–1997	Scotland, UK	7986	Third-generation ELISA	1.5%
Gunn *et al.*, 2001[58]	1998	San Diego, USA	615	Third-generation ELISA	3.4%
Tedder *et al.*, 1991[51]	1987	London, UK	1074	ELISA RIBA	2.6%

this is to be expected given the higher prevalence in men and the healthy volunteer effect among blood donors.

Rates of HCV are slightly higher than those that might be expected in the general population, although comparison is difficult because estimates for prevalence in the general population are clearly limited. In particular, antenatal and blood donor populations are both likely to be under-estimates. Importantly, the absolute differences between the UK prevalence studies and best estimates for the population prevalence are not substantial.

Studies of HCV-positive GUM clinic attenders demonstrate the importance of injecting drug use as a risk factor in this setting. A study in Scotland[54] (see *Table 7*) of the prevalence of anti-HCV among GUM clinic attenders found a 0.6% prevalence among homosexual and bisexual males, 0.8% among heterosexual males, 0.3% among heterosexual females and 48.6% among IDUs. These findings, in a country with a high prevalence of infected IDUs, demonstrate that sexual transmission may have been over-stated as a route for infection and show that the majority of cases of HCV encountered in GUM clinics are associated with IDUs.

IDUs are more likely than other groups to use GUM services.[59] The NSSAL[47] reported 2.2% of males and 2.9% of females who attended GUM clinics in the past 5 years had also injected drugs in the last 5 years. This compared to 0.4% of men and 0.2% of women who did not attend a GUM clinic. Of those who had injected drugs in the past 5 years, 17.8% of men and 29.5% of women attended a GUM clinic in the past 5 years.

There seems, therefore, to be limited evidence to support the use of GUM clinics as a setting to reach people at high risk of HCV with the exception of drug users.

Other routes of infection

Vertical transmission (from mother to child) occurs in 5–6% of pregnancies among infected women and infection is acquired by the child.

The risk of infection between cohabitees is, like sexual transmission, an area of ongoing debate and uncertainty. In a recent systematic review, Ackerman and colleagues calculated a pooled prevalence of 4% among siblings and household contacts of people with HCV-related chronic liver disease compared to 0% in controls.[60] This result was not statistically significant and the meta-analysis does not report on how potential confounding was handled in individual studies, suggesting the point estimate may be an over-estimate.

In 10–40% of cases of HCV, no known risk factor can be identified. This leaves scope for continued

TABLE 7 *Prevalence of HCV by subgroups of sexual orientation, gender and injecting drug use*[54]

Subgroup of GUM clinic population	Number in subgroup	Number infected with HCV	Prevalence of HCV in each subgroup (%)	Percentage of overall HCV prevalence accounted for by each subgroup
Homosexual/bisexual men (non-injecting)	668	4	0.6 (95% CI, 0.2 to 1.5)	3.4 (95% CI, 0.9 to 8.5)
Heterosexual males (non-injecting)	4135	32	0.8 (95% CI, 0.5 to 1.1)	27.1 (95% CI, 19.1 to 35.1)
Heterosexual females (non-injecting)	3035	10	0.3 (95% CI, 0.2 to 0.6)	8.5 (95% CI, 4.1 to 15.0)
IDUs (male and female)	148	72	48.6 (95% CI, 40.4 to 57.0)	61.0 (95% CI, 52.2 to 69.8)
Total	7986	118	1.5	100

debate about the role of potential routes for transmission, such as acupuncture, tattooing or ear-piercing, for which no conclusive evidence appears to be available.[61]

Summary of the natural history and epidemiology of HCV

- The natural history of HCV is characterised by high rates of chronicity and, after a long but variable latent period, clinically important sequelae.
- Injecting drug use is the most important route for infection with HCV in 2002.
- Sexual transmission does not appear to be an effective route for HCV transmission and number of sexual partners or sexual orientation do not appear to be important determinants of infection risk.
- Prevalence of HCV among IDUs is high. The unlinked anonymous prevalence survey estimates prevalence among drug service users as 32%. This is lower than some community-based studies in the UK, but reflects the prevalence among those in contact with drug services.
- GUM clinic attenders do not have a markedly higher prevalence of HCV than the general population and the majority of those found to be infected in this setting have a history of injected drug use.

QoL and HCV disease

There is a general perception that HCV is a slowly progressive, asymptomatic, ill-defined condition and has little impact on QoL.[62,63] HCV may not be detected until the later stages of disease and the acute infection with HCV is usually milder than with hepatitis A virus or HBV.[64]

However, a number of studies have reported non-specific symptoms associated with HCV, such as fatigue, abdominal pain, irritability, nausea, anorexia, muscle ache, headache, joint pain and right upper-quadrant pain.[63,65–67] It is increasingly reported that early stages of HCV are associated with symptoms and that patients do experience reduced QoL.

The perception that HCV is asymptomatic is challenged by health-related QoL (HRQoL) studies. Instruments, such as the SF-36, Sickness Impact Profile and disease-specific tools, have been used to measure QoL in those with HCV. The SF-36 is derived from the Medical Outcomes Survey, and contains eight subscales that evaluate the degree of impairment a person suffers in comparison to ideal health.[68]

HCV has been demonstrated in various studies to be associated with significant reductions in QoL,[69] and reductions have been noted in five to eight of the SF-36 subscales.[62,64,67] This reduction has also been found when compared to healthy UK controls.[70] Greatest impacts on QoL have been noted for role-physical, general health and vitality subscales of the SF-36.[67] Even mild liver disease (with absence of cirrhosis) has been associated with appreciable decrements in health utility and QoL.[71–73] Reductions in QoL associated with HCV infection are clinically and socially relevant.[64]

Recent studies have shown a reduction in QoL for patients with HCV similar to severe and chronic diseases. Patients with HCV scored significantly lower on QoL than patients with hypertension, and have similar or lower QoL than patients with non-insulin-dependent diabetes mellitus.[62,64] Patients with HCV, however, scored significantly better than patients with depression on the subscales related to emotional well-being.[62] Patients who progress to decompensated cirrhosis have recorded utilities similar to those suffering from stroke and mild dementia.[72]

It is possible that the reduction in QoL for these patients is a function of their co-morbidities (e.g. injected drug use, numerous blood transfusions or low socio-economic status). However, these patients have been shown to have a lower QoL than those without HCV even when adjusting for co-morbidities.[64,73] A relationship has been demonstrated between the eradication of HCV and QoL. Response to interferon treatment has led to improvement in QoL,[67,74] and the extent of improvement is related directly to sustained viral/biochemical response to treatment.[64] The SF-36 subscales most affected by treatment were related to perception of general health, vitality and social functioning, and to disease-specific scales concerning feelings of health distress and limitations caused by the infection with HCV.[64,67]

Studies have demonstrated that patients treated with interferon improve in all QoL measures (except eating) when compared to untreated HCV patients,[69] although reduced QoL on treatment is commonly seen.[67,69,75] Patients receiving combination therapy (interferon plus ribavirin) demonstrated slightly greater improvements in HRQoL than patients receiving interferon monotherapy, shown in the areas of vitality, social functioning, health distress and general health.[75]

It has been suggested that reported improvements in HRQoL following treatment may result in reductions in disability, for example, improvements in

the performance of daily tasks and handicap, such as working without limitations.[67] These improvements may also result in reduced demand for healthcare services and increased productivity in employment for people with HCV.[75]

Summary of QoL and HCV

- Despite the perception that HCV infection is asymptomatic, studies have reported non-specific symptoms associated with chronic uncomplicated HCV infection.
- People with HCV have been shown to have reduced QoL, even those with mild disease and when adjusting for co-morbidities.
- Patients with HCV have similar or lower QoL than patients with non-insulin-dependent diabetes mellitus.
- Antiviral treatment appears to improve QoL.

Chapter 2

Methods for the assessment

The assessment incorporated several elements.

- A systematic review of existing economic evaluations of screening programmes.
- A systematic review of the evidence of effects on behaviour associated with HCV transmission of gaining knowledge of HCV status.
- A survey of current practice in HCV screening in GUM clinics, drug services or prisons and of awareness of screening among health authorities (HAs).
- A model of cost-effectiveness of screening in drug services or GUM clinics.

This section details the methods used in each of these components.

Review of existing economic evaluations of screening programmes

A systematic review of existing economic evaluations of HCV screening programmes was conducted. A broad search strategy was carried out as preliminary searches suggested that there would be no RCTs of screening programmes and that the number of existing evaluations would be low.

The search strategy used is shown in appendix 1. No language restrictions were imposed. The references of identified articles were examined for further relevant studies. Members of the external advisory group and the manufacturers of treatments for HCV (Schering-Plough Ltd) were asked if they were aware of any further evaluations of screening programmes.

Papers that were reviews of evaluations of screening, debates on the value of screening or studies concerned with serological screening of blood donations were excluded.

The titles and abstracts of identified articles were checked for relevance by two researchers (KS and PR), and disagreements were resolved through discussion. The inclusion and exclusion criteria were applied by one researcher (KS). Appraisal of articles was conducted using the framework proposed by Drummond and colleagues.[76]
A narrative synthesis of studies was conducted.

Effect of knowledge on risk behaviour

Search strategies

The focus of this aspect of the assessment was on behavioural changes associated with gaining knowledge of HCV status. Initially, it was proposed that the search on this issue be extended to include HBV and HIV. However, on the advice of the external advisory group, it was concluded that HIV studies examining this issue would be of extremely limited relevance to the HCV-infected population. In particular, the view was taken that knowledge and attitudes to HIV are substantially different from HCV and this would severely limit the value of any extrapolation. The search was, therefore, restricted to studies focusing on HCV.

Electronic databases were searched using the strategies shown in appendix 1 and further relevant strategies were sought through citation searching, scrutiny of the references obtained and by seeking the advice of experts in the field.

Inclusion criteria and quality assessment

Studies were included if the intervention was knowledge of HCV status and outcomes were any behaviour associated with risk of HCV transmission (predominantly drug equipment sharing and sexual practices).

A methodological hierarchy was defined of study designs that might address the research question as follows (from high quality to low quality).

- RCTs of offering HCV testing with outcome of behaviour change between groups according to knowledge of status (HCV positive, HCV negative or HCV unknown).
- Cohort studies in which behaviour change was reported at baseline and following the offer of HCV testing.

- Cross-sectional studies comparing reported behaviour according to knowledge of HCV status (HCV positive, HCV negative or HCV unknown).

Inclusion criteria were not defined in relation to methodological quality as preliminary searches indicated that the volume of studies would be low. Rather, all relevant studies were included and the threats to internal and external validity according to the design used were discussed.

References and abstracts were assessed by one researcher (KS) for potential relevance. Methodological quality was assessed by one reviewer (LM) and checked by a second researcher (KS).

Study of current practice in HCV screening (diffusion study)

In October 2001, a questionnaire survey of GUM clinics, drug treatment services, HAs and prisons was undertaken to describe screening for HCV in England. All GUM clinics, HAs and prisons in England were included along with a 50% sample of drug services. Prisons were included, although outside the main scope of this review, to inform work being conducted by one of the researchers (JH) in collaboration with HM Prison Service. The study was endorsed by the office of the NSC prior to the protocol being developed for this assessment. Descriptive analysis is reported here.

The questionnaire was developed by two researchers (JH and KS) in collaboration with two hepatologists (Dr William Rosenberg, University of Southampton and Dr Matthew Cramp, University of Plymouth) and was piloted in each of the different types of organisations surveyed.

The questionnaire (see appendix 2) covered the following issues:

- how and when screening started
- the process of screening, including counselling, screening tests used and eligibility for treatment
- availability of data on the number of people screened and the outcomes of screening
- the reasons why organisations did or did not screen and what had influenced their decision.

A sampling frame was developed for the survey using sources outlined in *Table 8*.

One reminder letter was sent to non-respondents after 4 weeks. Data were entered into a Microsoft Access database (Microsoft Corporation, Washington, USA) for analysis.[77] The analysis was carried out by individual setting.

Cost-effectiveness model

A model of screening was developed in Microsoft Excel (Microsoft Corporation, Washington, USA). The structure of the model followed those previously published on screening and treatment in a previous rapid review.[78] The model examines the progress of hypothetical cohorts, passing through the stages of screening, diagnosis and treatment.

Perspective

The perspective of the model was the NHS.

Type of model and main assumptions

The screening model investigated a case-finding approach to screening in two populations: IDUs in contact with drug services and GUM clinic attenders. The approach was probabilistic and yielded an estimate of cost–utility (£/QALY) of screening versus not screening. The model examined a single round of screening in hypothetical cohorts from each population, that is, a prevalent round of screening. It, therefore, did not address the issue of screening interval, taking account of the risk of re-infection in screened individuals,

TABLE 8 *Sources used to identify the survey sample*

Sample	Source	Access date
Drug services identified as providing needle exchange services	Drugscope database (http://www.drugscope.org.uk/drugbaseii/search.asp), formerly the SCODA database	September 2001
Prison establishments	Prison service database (http://www.hmprisonservice.gov.uk/prisons/)	September 2001
GUM clinics	National AIDS Manual Database (http://www.aidsmap.com/search/orgsearch.asp?orgsearch=UKClinics)	September 2001
HAs	NHS Executive Offices, NHS Directories	September 2001

nor of repeated offers of screening to individuals who initially decline invitation. In the case of screening in drug services, it was assumed that only people who are not currently injectors would be eligible for treatment (following current recommendations for treatment[19]). In GUM clinics, where only a small minority of people presenting are IDUs, universal screening was assessed, that is, all people presenting would be considered eligible for screening. Overall, the model investigated the three main elements of the screening programme. The screening and diagnostic testing elements followed a simple epidemiological approach and the treatment element used a Markov chain model.

Screening

The offer of a serological test for HCV to asymptomatic individuals. If the offer of a screening test is accepted, a combination of an ELISA test followed by a polymerase chain reaction (PCR) to confirm presence of HCV RNA are carried out. The model sequentially applied values for the technical performance (sensitivity and specificity) of these tests.

Diagnosis

People who are HCV RNA positive after ELISA and PCR tests are offered liver biopsy. Rates of acceptance and estimates for the frequency of complications of liver biopsy were included. The results of liver biopsy determine eligibility for treatment.

Treatment

The treatment element begins with the number of patients who are likely to be deemed eligible and will accept treatment, following the findings of the liver biopsy. The treatment element of the model followed a Markov chain process running on an annual cycle. The cohort of patients in the treatment spreadsheet were assumed to be 32 years of age, based on evidence presented by Serfaty and colleagues.[79] The proportion of males and females were assumed to be equal. The model ran for a period of 50 years. It aimed to predict the natural history of disease, the health states through which the cohort passed, how long they spent in each state and the NHS costs of treating these patients identified through screening. Transition probabilities for each year of the cohort were estimated from a range of studies, which are detailed in the previous assessment report of interferon treatment[78] and summarised in the Effectiveness of treatment for HCV section of the results chapter on page 32. Death rates from unrelated causes were estimated from life tables of Great Britain.[80]

The screening and diagnostic elements of the model are outlined in *Figure 2*, which also shows assumptions regarding additional health service usage during these stages. People who reach the final stage in the screening and diagnostic elements move onto the treatment element, which is shown in *Figure 3*. In the treatment model, the natural history of infection was simulated for those people who respond to treatment, and in whom sustained viral clearance was assumed to indicate eradication of infection. The cost-effectiveness of treatment was calculated from the sum of QALYs in health states avoided and costs associated with treating these states. A detailed description of the estimates used in the model is given in the Cost-effectiveness model section of the results chapter.

Screening was compared to a no screening scenario, in which people with HCV would have presented for treatment 11 years later with symptoms. This period was taken from the difference in mean age between patients enrolled in screening studies[79] and those enrolled in treatment for HCV RCTs.[81]

The net cost per QALY was derived by summing the associated costs (or savings) and benefits (or disbenefits) from screening, follow-up and treatment. Methods for identifying estimates are outlined in the Cost-effectiveness model section of the results chapter on page 29, and estimates are presented in detail in tables within this section.

The following parameters were included in the model.

1. Screening

- Prevalence of HCV in target population.
- Proportion of people eligible for screening.
- Acceptance of screening and biopsy.
- Screening test performance.
- Costs of screening test and biopsy.
- Harms of biopsy and associated costs.
- Costs of counselling before and after screening test.
- Eligibility for treatment with combination therapy.
- Acceptance of treatment.

2. Management received by those who drop out of the model (negative results or lack of adherence)

- Cost of follow-up outpatient visits they receive.
- The number of years that patients with mild or severe disease will be monitored through outpatient attendance.
- The number of years that patients with moderate disease (who refuse treatment) will receive outpatient visits.
- Attendance rate at outpatient visits.

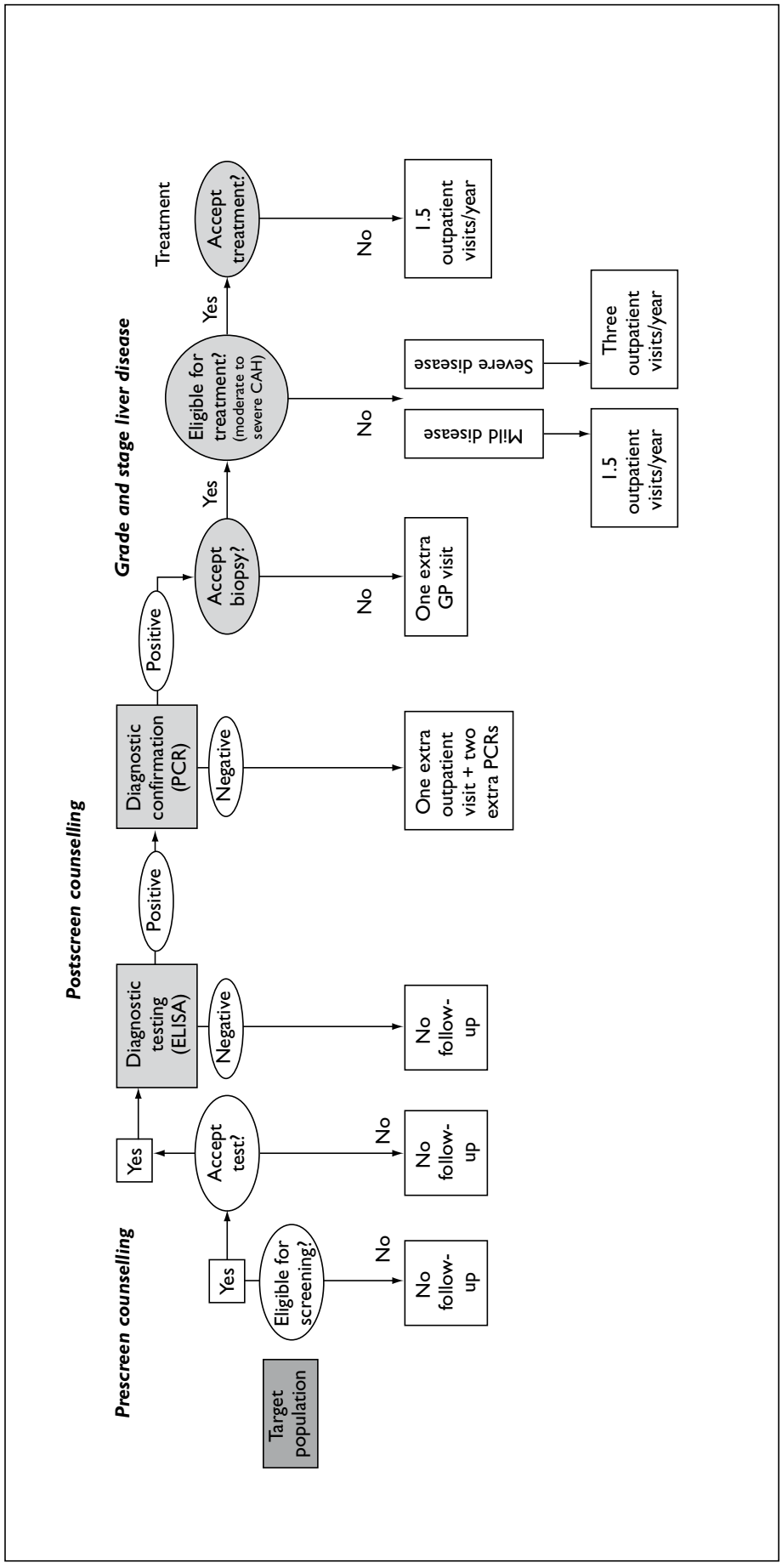

FIGURE 2 *Screening and diagnosis elements of the model*

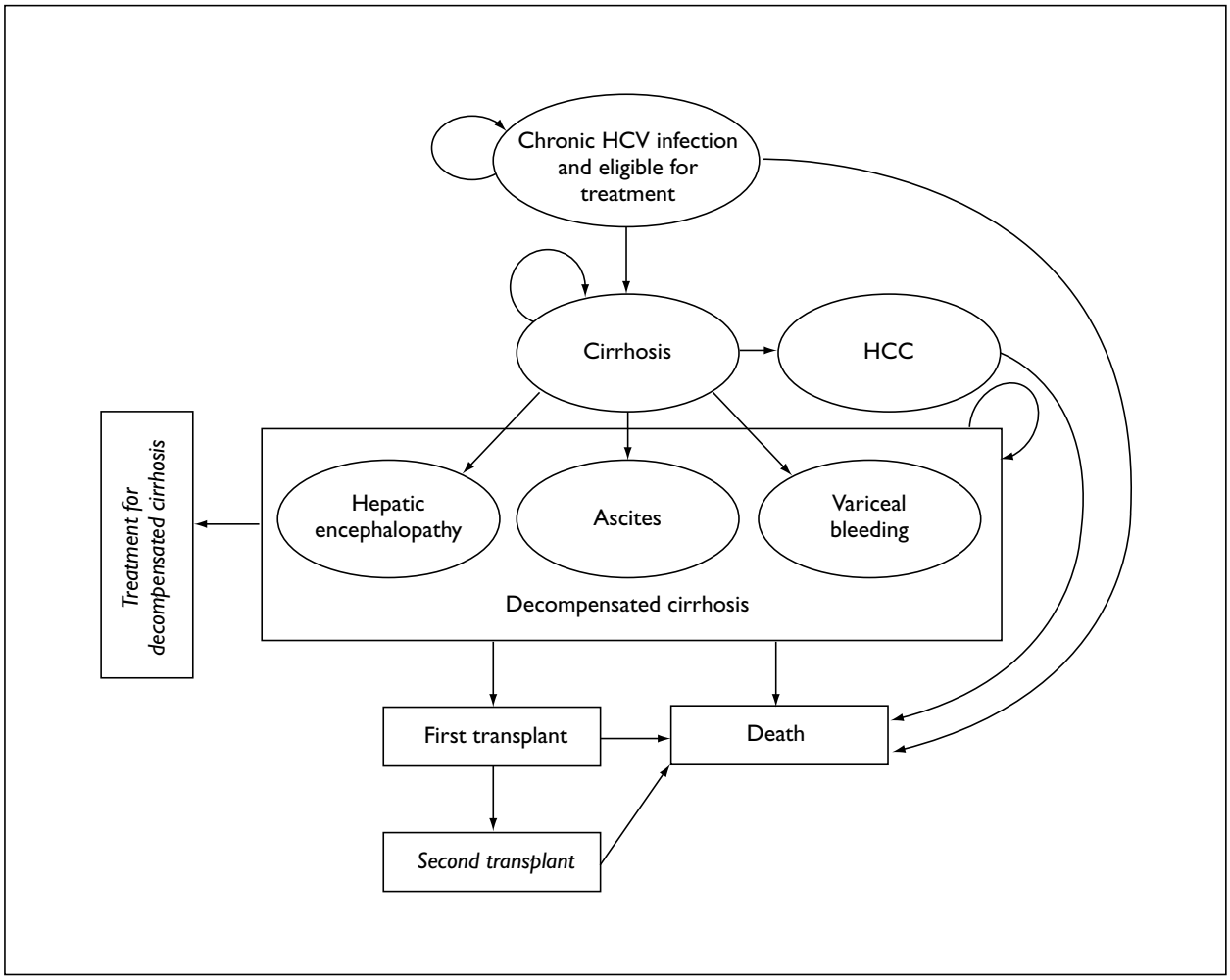

FIGURE 3 *Health states included in the treatment element of the model*

3. Treatment with interferon plus ribavirin combination therapy

- Probability of sustained viral response to treatment, that is, apparent clearance of HCV.
- Progression rates from moderate chronic HCV disease to cirrhosis and its complications of ascites, variceal bleeds, hepatic encephalopathy, HCC and death in the absence of treatment.
- Cost associated with treating these states (except death).
- Probability of receiving first and second liver transplants and associated costs.
- Costs of general practitioner (GP) and outpatient attendances.
- Costs of combination therapy.
- Utilities associated with possible health states (drug treatment, chronic hepatitis, cirrhosis, ascites, hepatic encephalopathy, variceal bleeds, HCC, liver transplant and successful drug treatment).
- Probability of adverse effects on combination therapy and associated utility.

Sources for estimates

A range of literature searches was conducted to identify values for the parameters included in the model (see appendix 1). It was beyond the scope of the assessment to carry out exhaustive systematic reviews to inform each of the parameters in the model. For the base-case estimates, values were chosen from studies on the basis of methodological quality of the study, how recently the study was published, the relevance to the UK setting, the generalisability of the study population to the current question and the sample size of the study. Where possible, existing systematic reviews of good quality were used (see the Cost-effectiveness model section of the results chapter on page 29 for a description and justification of base-case estimates and tables within this section for a summary). The model by Shepherd and colleagues[78] used in the NICE appraisal of the cost-effectiveness of treatment was used to estimate the benefits and costs associated with treating people found to be HCV positive on screening.[78] A further search was performed forwards from

that review (years 2000–2001) for relevant studies. The same search strategy and inclusion and exclusion criteria as the previous assessment were used,[78] seeking further RCTs and systematic reviews. Two recently published systematic reviews on the effectiveness of therapy[82,83] were reviewed. The Shepherd and colleagues model[78] was updated by revision of cost data obtained from a range of routine sources.

Discounting

Costs were discounted at 6% and benefits at 1.5% in the base-case analysis.

Sensitivity analysis

Extensive one-way sensitivity analysis was conducted to identify those estimates in which uncertainty has the greatest effect on the overall estimate of cost–utility for screening for HCV. For screening in GUM clinics, three multi-way analyses of selective screening strategies were carried out.

Given the long timescale involved in accruing benefits from screening and treatment, the effects of increasing the discount rate for benefits to 3% and 6% were explored in sensitivity analyses.

Chapter 3
Results

Existing economic evaluations of screening programmes

Nine studies were found that appeared to be evaluations of screening programmes and which were examined in detail.[84–92] Details are shown in appendix 3.

Three of the studies were excluded. The studies by Roque and colleagues[92] and Fischer and colleagues[89] were descriptions of the performance of risk assessment tools in identifying people with HCV and did not include any economic evaluation. The study by Perez[91] was a description of screening in an anonymous screening centre in France and contained no economic evaluation.

Descriptions of the included studies are shown in *Table 9*. Two of the six included studies aimed to be comprehensive evaluations of screening programmes, that is, to integrate information on all stages of screening, diagnosis and treatment to reach an overall assessment of value for money. One of these was a cost–utility analysis (CUA), which this technology assessment extends.[84] The other was described as a cost–benefit analysis of a screening programme established in Japan.[85] The other four studies examined the performance of screening tests in identifying people with HCV and presented estimates for cost per case detected for a variety of screening strategies. Two studies were carried out in France[86,90] and two in the USA.[87,88] Only one of these studies, by Kaur and colleagues,[88] estimated the cost per durable response. All studies had significant methodological shortcomings and those performed outside the UK were of very limited relevance to screening for HCV in the UK healthcare system.

Ishizuka[85] carried out an economic evaluation of screening for HCV in the Saga area of Japan. Screening was instituted in 1993 as part of a general medical screening programme ("health project for the aged") and was offered to people aged 30–59 years of age. Details of the population involved and the settings for screening were limited. The prevalence of HCV was high (8.3%). Screening was conducted using second-generation ELISA tests followed, in those with high antibody titres, by liver biopsy. Treatment was with interferon monotherapy and complete response rate was assumed to be 30%. Future costs and savings were estimated using a simple model of disease progression, using mean times to progression between HCV-related health states stratified for age and sex. The benefit:cost ratio for screening was estimated to be between 1.3 and 3.1 and the authors concluded that screening was favourable where the prevalence of HCV positives was greater than 1%. Sensitivity analysis demonstrated the importance of discount rate and interferon response rate.

The analysis had several significant methodological limitations. The monetary valuation of benefits was restricted to avoided costs of treatment for

TABLE 9 *Description of included studies*

Study	Country	Type of study
Ishizuka, 1999[85]	Japan	Cost–benefit analysis of screening programme based on costs of screening and savings through averted costs of treating consequences of chronic HCV
Lapane *et al.*, 1998[87]	USA	CEA (cost per case detected) of different approaches to screening based on risk factors identified through the USA National Hepatitis Surveillance Program
Kaur *et al.*, 1996[88]	USA	CEA (cost per case detected and per durable response to treatment) of different approaches to screening. As Lapane *et al.*, 1998,[88] based on the USA National Hepatitis Surveillance Program
Desenclos *et al.*, 1997[90]	France	CEA of screening strategies for HCV, comparing ALT and risk factor-based approaches
Rotily *et al.*, 1997[86]	France	CEA of combinations of screening tests in different target populations
Leal and Stein, 1998[84]	UK	CUA of screening for HCV in IDUs and GUM clinics in southwest England

sequelae of HCV infection and loss of earnings. This approach to the valuation of benefits took no account of the preferences people may have had regarding the health states that treatment may have avoided. The model of disease progression was less sophisticated than the Markov approach taken in other studies of the cost-effectiveness of treatment and was not validated. Notwithstanding the general difficulties in reaching conclusions about the value of interventions based on studies conducted in different countries, the study demonstrated clear differences in management of HCV that severely limited the relevance to the UK, for example, 4-day admission for liver biopsy, 2-week admission for treatment with interferon.

Lapane and colleagues[87] and Kaur and colleagues[88] each described analyses conducted as part of the USA National Hepatitis Surveillance Program. This was established in 40 urban centres in the USA in 1992 and was advertised through a multimedia campaign. A total of 14,000 people responded to the invitation to come forward for HCV screening. Of this self-selected population, 9000 completed a risk profile questionnaire. Participants were screened by second-generation ELISA followed by recombinant immunoblot assay (RIBA) in positive cases. Alanine transferase (ALT) levels were also determined. The sample yielded a higher prevalence of HCV (7%) than estimates for the whole USA (1.8%).

Kaur and colleagues[88] calculated the cost of detecting a case of HCV, based on the cost of diagnostic tests and two medical consultations, as US$1246, which compared favourably to other screening programmes (e.g. colorectal and breast cancer screening). Based on the assumption that 75% of newly diagnosed patients would be treated with interferon monotherapy and that a durable response rate would be achieved in 10–25% of those treated, the cost per durable response was calculated at US$6233–15,764. However, this result should be treated with caution for the following reasons.

- Only the screening test and consultation costs were included – biopsy costs and costs of follow-up visits were excluded.
- The screening tests used (second-generation ELISA with RIBA confirmation) have been superseded.
- Adherence rates on treatment were assumed to be 100%.
- Harms of investigation and treatment were not considered.
- The perspective was the USA. Differences in the organisation of care and population acceptance of screening and treatment limit generalisability to the UK.

Lapane and colleagues[87] investigated the performance of four approaches to prescreening, that is, the identification of people at risk who might be offered screening.

(1) Based on a regression analysis of all risk factors, an individual risk prediction equation was determined and the characteristics of this investigated using a receiver–operator-characteristics plot (the balance between true- and false-positive rates at different cut-off values of risk). The best performing cut-off (7%) for risk was chosen as the criterion for screening.
(2) Serological testing in individuals at "significant risk" based on any positive response to questions that were grouped as "socially intrusive" (history of injected drug use or sex with an IDU) and "non-socially intrusive" (age 30–49 years, transfusion history and male gender).
(3) Serological testing in those at "significant risk" based on answers to two or more non-socially intrusive questions.
(4) Serological testing based on abnormal ALT levels.

The sensitivity, specificity, predictive values and marginal cost per case detected of these strategies were reported. Model (1) performed best, leading to screening of 20% of the population and being more effective and less costly than model (3), which was used as the base case in the economic analysis. The average cost per case detected in model (1) was US$357, although the analysis was methodologically weak and of limited relevance to the UK. The ELISA tests used (second generation) have been superseded, cost estimates were limited to the cost of tests (counselling and consultation were not included) and there was no exploration of uncertainty in the results.

Desenclos and colleagues[90] evaluated screening (using third-generation ELISA testing confirmed by RIBA) carried out in France on 6238 social insurance beneficiaries. The evaluation compared the sensitivity, specificity, predictive value and cost per case detected of screening for HCV on the basis of reported risk factors or on abnormal liver function testing (ALT). The evaluation was of reasonable quality, although there are some areas for concern. The testing strategy identified people who had antibodies against HCV, which included a proportion who were no longer infected and,

therefore, not at risk of chronic HCV disease. The multivariate analysis used to identify significant risk factors was not described in detail and only the cost of diagnostic tests contributed to the cost per detected case analysis. Only assay costs were included – no allowance for counselling and medical consultations was made. Differences in service organisation and costing methods between the UK and France make it difficult to extrapolate the results.

Screening on the basis of any of the six risk factors with the highest specificity (IDU, five or more pregnancies, sexual partner of an IDU or HCV-positive person, household contact with HCV or more than one termination of pregnancy) resulted in 9.5% of the population being screened with a sensitivity of 53%, specificity of 91% and cost per case detected of FF2900. Screening only on the basis of history of injecting drug use or transfusion prior to 1991 was slightly more cost-effective, because only 8.8% of the population were selected for screening with a positive predictive value of 7.6% and cost per case detected of FF2400. Screening on the basis of abnormal ALT was based on a cut-off defined for the French population for screening of blood transfusions and was the most cost-effective option (FF1600), but is of limited relevance to the populations being considered in this assessment.

Rotily and colleagues[86] carried out a CEA based on a decision analysis model of different combinations of screening tests in a range of populations: general population, transfusion recipients, haemophiliacs, IDUs and haemodialysis recipients. Eleven combinations of tests were explored (except where indicated, tests were carried out in sequence):

- PCR
- PCR + PCR
- ELISA
- ELISA + PCR
- ELISA and ELISA in parallel
- ELISA + ELISA
- ELISA + RIBA
- ELISA + RIBA + PCR
- ALT
- ALT + ELISA
- ALT + PCR.

The study estimated the cost per true-positive case detected from the perspective of the French healthcare system, but had a number of important limitations. Costs were restricted to those of assays and one consultation with a GP. Average cost-effectiveness ratios were reported, so the effect of moving from one strategy to another was not demonstrated. The quality and precision of the estimates of test effectiveness were not described and there was no exploration of uncertainty in the effectiveness of tests. Sensitivity analysis was conducted by attaching different weights to outcomes other than true-positives.

When restricting the analysis to the number of true-positives detected, ELISA alone had the lowest average cost-effectiveness. However, the number of false-positives was high for this strategy (e.g. in screening the general population, over 3 million people would be misclassified as HCV positive). PCR followed by PCR gave the lowest number of false results but at high cost. The favoured strategy was ELISA followed by confirmatory testing (RIBA or PCR).

Leal and Stein[84] evaluated a prevalence round of screening in GUM clinic attenders and IDUs for the South and West Development and Evaluation Committee. The analysis of screening in IDUs has been published separately.[77] This study carried out an assessment of screening against recognised criteria[93] and included a model of screening which yielded an estimate of cost–utility. The clinical course of patients dropping out of the screening programme (either by lack of acceptance or negative tests) was assumed to follow that of the natural history of disease.

The cost–utility of screening was estimated at £10,177/QALY in IDUs and £27,125/QALY in GUM clinic attenders. Sensitivity analysis showed a range of possible cost–utilities: £12,580–194,026/QALY in GUM clinic attenders and £3333–81,438 in IDUs. Estimates were particularly sensitive to variation in adherence to liver biopsy and interferon treatment and to the effects of discounting benefits. A key limitation in this economic model was that people who were not identified through screening were assumed to follow the natural course of HCV disease. Furthermore, the analysis provided an average estimate for cost-effectiveness, but the competing alternative (no screening) was not explicitly addressed, that is, there was a tacit assumption that cases would not be identified other than through screening. This will have biased cost-effectiveness of screening downward. The authors noted other limitations in the model, particularly that life-years in health states of chronic HCV and related liver diseases were drawn from an earlier model that assumed similar natural histories for HBV and HCV. Very few data on adherence in the target populations were available, which, combined with the importance

of these parameters to the sensitivity of the model, resulted in a cautious conclusion regarding the value of screening. The South and West Regional Development and Evaluation Committee, which considered the report, provided the following guidance to the NHS locally:

> "although the evidence presented shows that a prevalence round of screening in intravenous drug users could be cost-effective, there is too much uncertainty surrounding this to reach a definite conclusion. In particular, the evidence relies on assumptions regarding the natural history of hepatitis C and likely adherence to diagnosis and treatment that may not be valid."

Summary: existing evaluations of the cost-effectiveness of HCV screening

- Two studies attempted economic evaluations of HCV screening programmes. One of these was a limited cost–benefit analysis in Japan and was not relevant to the UK. The other, which this assessment extends, was hampered by poor information on natural history and adherence to investigation and treatment and did not incorporate a comparison with no screening.
- Other evaluations of screening were restricted to the performance of prescreening risk assessments or were limited evaluations of the cost-effectiveness of the test component of a screening programme.
- Evaluations all had methodological limitations and/or were of limited relevance to the UK populations of concern.

Impact of knowledge of HCV status on behaviour

Studies included in the review

No reviews of the impact of knowledge of HCV status on behaviour and no studies that focused on populations other than IDUs were found. The studies identified as being of relevance are summarised in *Table 10* (see appendix 3 for further details).[94–97] Three studies were cross-sectional designs (low quality), and no high-quality studies were identified.

Cook and colleagues[94] used a cross-sectional design to examine associations between self-reports of previous HCV testing and risk behaviours of 385 IDUs recruited in northwest England from a variety of drug services and IDUs not currently in contact with drug services. Information on the following behaviours was obtained using a self-administered questionnaire:

- drug-related behaviour (ever or in the past 4 weeks), including drug-taking, sharing of needles and other equipment
- sexual behaviour, including the number of male and female partners ever and in the past 4 weeks and usual method of contraception.

Vidal-Trecan and colleagues[95] conducted a cross-sectional survey in France between 1994 and 1995 among 592 sexually active in-treatment individuals who were currently IDUs and compared risk behaviour of HCV seronegative individuals with that of HCV seropositives and HCV unknowns (defined as never tested or not tested within the previous 6 months). Individuals with severe mental disorders, AIDS, unable to answer questions or receiving methadone were excluded. Information was collected during a face-to-face interview on drug-related behaviour during the previous 6 months (use of new equipment, lending injecting equipment, borrowing injecting equipment and not using clean equipment) and sex-related behaviour (multiple partners over the previous 6 months, prostitution and not using condoms at last sexual encounter).

TABLE 10 *Studies identified on the impact of knowledge of HCV status on behaviour*

Study	Design	Population
Cook *et al.*, 2001[94] (northwest England)	Cross-sectional	IDUs: • in contact with drug treatment services (syringe exchange, outreach, inpatient) • not in contact with services, recruited via snowball sampling of initial recruits • self-referred to drug services for HCV testing
Vidal-Trecan *et al.*, 2000[95] (France)	Cross-sectional	Consecutive attenders at ten drug treatment facilities
Malliori *et al.*, 1998[96] (Greece)	Cross-sectional	Narcotic drug users, the majority currently IDUs, in two Greek prisons
Ompad *et al.*, 2000[97] (Maryland, USA)	Longitudinal	IDUs with a history of injecting of < 5 years recruited through drug treatment services and community outreach

Ompad and colleagues[97] carried out the only longitudinal study identified. Details of the study were obtained from the authors. They identified IDUs who were early in their injecting history (< 5 years of injecting) through community outreach and via drug treatment services. The sample included a high proportion of African-Americans and women were over-represented. After a baseline questionnaire on behaviours, subjects were screened for HCV and followed up at 6 and 12 months where changes in behaviours were assessed. Direct (needles) and indirect (cottons, rinse water, cookers and backloading) sharing were considered.

Malliori and colleagues[96] investigated associations with HCV infection in prisoners in two Greek prisons in a cross-sectional survey. Although not the main focus of the study, they reported an analysis of injection equipment sharing according to self-reported HCV status among participants who had had previous serological testing.

Results of the studies included in the review

The results of the included studies are presented according to the behaviours that were assessed in association with HCV testing and knowledge of status.

Effects of HCV knowledge on drug-related behaviour

Cook and colleagues[94] found no statistically significant differences in the following drug-related risk behaviours over the previous 4 weeks among IDUs who reported having had a previous HCV test compared to those who reported not being previously tested: sharing needles, syringes, spoons, filters and paraphernalia. However, a *post hoc* subgroup analysis showed that those who had previously taken an HCV test were more likely to be reformed sharers, that is, to have shared equipment in the past but not in the prior 4 weeks.

Vidal-Trecan and colleagues[95] found that people known to be HCV negative were more likely to use previously used equipment than people known to be HCV positive (OR = 2.0, 95% confidence interval (CI), 1.2 to 3.3) or people of unknown HCV status (OR = 2.5, 95% CI, 1.7 to 3.3). Unknown status was defined as having had no previous test or a negative test more than 6 months previously. HCV-unknown participants were more likely not to disinfect used equipment than those known to be HCV negative (OR = 1.9, 95% CI, 1.4 to 3.0). The behaviour of all those reporting previous HCV tests was not directly compared with those reporting no previous testing and raw data from which this could be calculated were not reported.

Ompad and colleagues[97] reported no significant differences between HCV-positive and non-HCV groups in sharing behaviour between baseline and follow-up. Across both groups, only 10% reported no change in needle sharing with 23% reporting an increase and 17% reporting a decrease.

Malliori and colleagues[96] reported no significant differences in equipment sharing during the last month between those known already to be HCV positive and those who reported a negative HCV test in the past (39 versus 37%).

Effects of knowledge of HCV status on sex-related behaviour

Vidal-Trecan and colleagues[95] found that those with unknown HCV status were significantly more likely not to use condoms at the last sexual encounter than those who reported a previous HCV-negative test result (OR = 2.9, 95% CI, 1.9 to 4.6). No statistically significant differences were found between those with unknown HCV status and those reporting a previous HCV-negative result in either number of individuals having multiple sexual partners or the number reporting prostitution.

Methodological issues

All the studies identified had methodological shortcomings. Cross-sectional studies cannot detect whether an association between HCV knowledge and behaviour is causal. Without controlling for pre-test behaviour, it is possible that the absence of any difference in post-test behaviour between seropositive and seronegative individuals may conceal a reduction in the high-risk behaviour of the seropositive individuals.

Experimental designs of the effect of virological testing on behaviour, that is, where people are randomised to screening and behavioural change compared to those not screened, are feasible and have been conducted in HIV research.[98] An alternative design would be a longitudinal study of behaviour with data collected at a number of timepoints before and after the acquisition of knowledge of HCV status. No study that followed either design was found; although there was one longitudinal study, this collected information at only one timepoint (at the time of testing) with later follow-up.

All studies of risk behaviours are subject to social desirability bias, that is, respondents are more likely to make responses that are held to be more

acceptable by society in general. The importance of this bias increases where there are particularly strong social norms around behaviours, or where behaviours are illegal in the society concerned and are clearly a concern in this area. Self-reports may not be stable over time. For example, Greenfield and colleagues[99] found that self-reports of abstinence from cocaine and heroin use were less likely to be confirmed by urinalysis at 6 months than at baseline. No reasons for the decline in validity of self-report were found and Greenfield and colleagues' suggestions for the findings included participants being less motivated to be accurate over time, under-reporting of behaviours to shorten interviews or subjects under-reporting risk behaviours as the study progressed due to unknown factors.

As the behaviours of interest in the studies identified could not be confirmed by objective methods, the effects of social desirability bias cannot be investigated. In the studies by Vidal-Trecan and colleagues and Cook and colleagues, researchers were present at the time when questionnaires were completed. These steps may have presented an opportunity to reassure participants about confidentiality and the need for accurate responses. On the other hand, the presence of researchers may have led to more biased responses. The Ompad and colleagues and Malliori and colleagues studies did not report steps taken to reduce this source of bias.

Recall bias is a potential problem for all the studies identified, not least because of the potentially amnesic effects of drug and alcohol use. There is some evidence of the possible effects of recall bias. In the studies by Cook and colleagues and Malliori and colleagues, there were actual or potential discrepancies between self-reports of HCV status and serological results. In the study by Cook and colleagues, 18% of those previously tested could not recall the result and in 16% there was a discrepancy between reported and actual serostatus. In the study by Malliori and colleagues, over 54% of the sample reported a previous HCV serology test and 9% reported this to have been positive. The seroprevalence study carried out by Malliori and colleagues reported anti-HCV-positive prevalence of 58% overall and 80% in IDUs. It is possible, although unlikely, that a discrepancy of this size was due to new infections since testing rather than poor recall of previous testing and results.

Vidal-Trecan and colleagues categorised participants as equipment lenders or sharers on the basis of self-reported history of the previous 6 months, a relatively long period for recall.

Although Ompad and colleagues conducted the only longitudinal study in this area, recall bias cannot be excluded. Participants were asked to recall equipment sharing in the 3 months prior to the study and at 3-month follow-up. Participants may have had better recall of the 3 months following the test in expectation of being asked to report behaviours again. This study was further limited by the small sample size, raising the possibility of false-negative errors in the findings, and by limited generalisability to longer-term IDUs and the UK population.

Weinstein and colleagues[100] identified further methodological and conceptual errors in research involving the use of correlational data to examine the effect of risk perceptions on precautionary behaviour in 81 analyses from 59 studies in HIV prevention, which may apply to the current review. Tremendous diversity was found in the variables and designs used to investigate the same issue and problems were characterised as follows.

- The **causal inference problem** refers to the misinterpretation of correlations from cross-sectional studies as testing the motivational hypothesis when they actually measure the accuracy of risk perceptions. Longitudinal data are necessary to test for actual behaviour change.
- The **prior behaviour problem** refers to the lack of control for previous behaviour either statistically or by restricting the sample to individuals with the same initial behaviour. Questions of perceived risk and behaviour intention are only valid if the risk perception questions refer explicitly to the continuation of current behaviour. Unless this is explicitly specified, subjects might incorporate intended behaviour changes into their initial risk perceptions.
- The **behaviour stability problem** occurs when prospective studies do not take into account the change in correlations between perceived risk and subsequent behaviour that is likely between the time of first awareness of hazard to the time when individuals have had years to change their behaviour.

Summary – HCV knowledge and behavioural change

- Few relevant studies addressed the question of interest.

- Relevant studies had considerable methodological limitations.
- There was no compelling current evidence to support the idea that behavioural changes would occur as a result of learning HCV status, either among those shown to be HCV positive (who may be encouraged to reduce the risk of infecting others) or those who are shown to be HCV negative (who might consider protecting themselves from infection).

Study of current practice in HCV screening (diffusion study)

This section reports the main results of the diffusion study. Further details of the results of the study are given in the summary tables of responses in appendix 4.

Response rates

A total of 597 questionnaires were sent and 386 returned giving an overall response rate of 65%: 73% of HAs, 63% of prisons, 61% of drug services and 64% of GUM clinics responded. Twenty-eight responses were invalid for the following reasons: moved/unknown address (n = 8), no clinical service provided (n = 3) and duplicate response (n = 17).

Prevalence of screening

Participants were asked if screening for HCV was conducted by their organisation, or, in the case of HAs, in their area. A minority of HAs and drug services reported screening in their area/service (28 and 26%, respectively). In contrast, most prisons and GUM clinics that responded reported screening for HCV (78 and 92%). Screening was most prevalent in GUM clinics.

Little information was provided by organisations on when screening started other than prisons, who reported a bimodal pattern of screening diffusion over the past 10 years, with peaks in 1996 and 1999, when 13/34 prisons started screening.

A minority of organisations, which were not screening, had taken an active decision not to screen, that is, where screening was not in place, there had been no explicit consideration of screening. Fifteen of 50 (30%) HAs that reported that they did not currently screen had considered it, as had eight of 52 (15%) drug services.

Eligibility criteria for HCV screening

Across all respondents, the majority reported offering screening only to people who presented with identified risk factors, that is, the first step in screening was to establish eligibility for the offer of a screening test. Twelve of 19 (63%) HAs reported selective screening, as did 19 of 66 (29%) prisons, eight of 18 (44%) drug services and 95 of 123 (77%) GUM clinics. Universal screening was reported by 29% of prisons, 11% of drug services and 7% of GUM services.

Some organisations reported that they screened only at the request of the client (prisons 16/66, GUM clinics 11/123 and drug services 5/18), despite these organisations having clearly indicated that they conducted screening as defined for the survey. There were at least two possible reasons for this apparent ambiguity. Respondents may have indicated that screening and testing on request were both available in their organisation or that the screening would only be carried out with the consent of the individual. One prison and one HA did not know the eligibility criteria for their organisation.

The most common eligibility criteria employed by organisations were drug use (prisons 71%, GUM clinics 67%, drug services 57% and HAs 33%) and sexual behaviour (prisons 15%, GUM clinics 21% and drug services 7%). No HAs reported sexual behaviour as an eligibility criteria. There was significant variation within these categories. There was considerable variation and lack of clear definition of eligibility criteria across and between organisational types.

Repeat screening and screening intervals

The majority of prisons (67%), drug services (78%) and GUM clinics (76%) offered repeat screening to those eligible. HAs reported offering repeat screening in 37% of responses, although there was a large amount of missing data (37%).

The majority of prisons (61%) and GUM clinics (61%) that reported offering repeat screening reported a defined interval before which re-screening would not be offered. In contrast, the majority of HAs (71%) and drug services (71%) reported no defined screening intervals. Screening intervals varied within and between organisation types. In 12 cases (one HA, one prison, two drug services and eight GUM clinics), screening interval was defined as a range, for example, 1–6 months.

The two most frequently listed reasons for the choice of interval were the "window period", that is, the period between infection and development of detectable antibodies to HCV, and reasons relating to the risk behaviours of the people

presenting to their service, although no further specification was given in the latter category.

Influences on the decision to start screening

Organisations were asked who was involved in the decision to start screening. HAs responded that most often the HAs (23%) and drug services (17%) were involved. Many HAs reported that three or more organisations were involved in the decision to commence screening (8/13), for example, prison health officers, the HA and clinicians.

Many prisons (56%), drug services (45%) and GUM clinics (64%) reported that their own organisation was involved in the decision to start screening. In addition, many reported that their local HAs were involved in the decision (prisons 31%, drug services 35% and GUM clinics 18%). A smaller number reported the involvement of medical officers (prisons 0%, drug services 16% and GUM clinics 2%). The majority of GUM clinics (89/110) reported that the decision to start screening was made by one organisation only, as did the majority of prisons (45/64). The decision was most frequently made in drug services by one or two organisations.

Organisations were also asked about influences on the decision to start screening on a scale of 1 to 4 (1 = very influential and 4 = not influential). The following were assessed: public and patient views, professional views, national policy, regional policy, evidence for effectiveness and value for money (cost-effectiveness). Across all organisational types, professional views were the most influential. Cost-effectiveness was the least influential factor for all organisational types except HAs.

Participants were also asked what sources of evidence for effectiveness or cost-effectiveness informed the decision to start screening. There was no consistent trend in terms of the sources of evidence that organisations reported using. Relatively few respondents provided answers to this question, and in GUM clinics and prisons a number reported that they did not use any sources of evidence (22 and 38%, respectively). HAs reported consulting the literature (40%), public health departments (20%) and NICE/NHS/Department of Health guidance (20%). Prisons most often reported consulting other centres (12%). Drug services did not consistently report any one source, and GUM clinics most often reported experience/opinion/colleagues as their source of evidence (31%).

Screening tests used

A variety of serological screening tests were listed by organisations that reported screening for HCV. The tests included antibody testing, which was not further specified, ELISA tests and combinations of antibody testing and RIBA. ELISAs were the most frequently reported screening test. Many organisations reported that they refer clients to other organisations to be tested and, therefore, did not know the type of test used. PCR was most frequently cited as the test used to confirm presence of HCV RNA, although responses were limited to this question, which might have been more comprehensively answered by inclusion of virologists in the survey.

Information given to people at the time of screening

Participants were asked to list the type of information given to people at the time of screening. The most common information provided was on prevention and risks (HAs 25%, prisons 13%, drug services 15% and GUM clinics 21%), counselling (HAs 25%, prisons 29%, drug services 18% and GUM clinics 10%), disease information (HAs 0%, prisons 14%, drug services 15% and GUM clinics 17%), treatment (HAs 0%, prisons 5%, drug services 13% and GUM clinics 13%) and the implications of a positive test result (HAs 8%, prisons 14%, drug services 10% and GUM clinics 14%).

How people are informed of their test result

The majority of HAs, prisons, drug services and GUM clinics reported that people who were HCV negative were informed of their result when they returned to the service (47, 39, 61 and 57%, respectively). Some prisons reported informing people of their negative test result in person (30%), and some GUM clinics reported that they either informed people when they returned or by telephone (28%).

The same pattern was reported for informing people of a positive HCV result. The majority of organisations that responded reported that they informed people of their positive test result when they returned to the service (HAs 42%, prisons 42%, drug services 61% and GUM clinics 77%). In addition, a number of prisons specified that they inform of a positive result in person (32%).

Treatment of HCV

Treatment for HCV was known to be available in 74% of HAs, 58% of prisons, 78% of drug services and 65% of GUM clinics. Availability of treatments

for HCV was investigated. The majority of all organisational types reported that combination therapy with interferon plus ribavirin was used as treatment (HAs 74%, prisons 48%, drug services 61% and GUM clinics 57%). Pegylated interferon was reported as being available by some members of all organisational types (HAs 21%, prisons 18%, drug services 28% and GUM clinics 32%).

Eligibility criteria for treatment

The majority of organisations who screen for HCV reported that eligibility for treatment is limited (HAs 74%, prisons 50%, drug services 67% and GUM clinics 43%). Very few organisations (3.5%) reported no eligibility criteria, although 47% did not know or did not respond.

There was considerable variation in descriptions of eligibility criteria, which may be due, in part, to different levels of detail in reporting in response to an open question. Severity of liver disease and drug/alcohol use were cited most frequently, with variation in the detail of eligibility criteria, such as length of abstinence, alcohol consumption threshold or requirements regarding methadone treatment. Many organisations, particularly GUM clinics, reported that criteria were applied elsewhere, by the centre to which clients were referred for testing.

The findings suggested that specific knowledge of treatment criteria in organisations conducting screening may be limited, particularly where treatment is instituted elsewhere. Distance between screening and treatment services may mean that screening is offered to some clients in whom treatment would not be considered. Alternative reasons for screening in these circumstances may be:

- to offer monitoring of disease progression and consider treatment if eligibility changes
- to encourage harm reduction in relation to HCV progression (e.g. reduction of alcohol consumption)
- to encourage behavioural changes to reduce risk of HCV transmission
- because knowledge of status may be considered to have intrinsic value.

Organisations that do not currently screen

The majority of HAs and drug services reported no screening in their area/service (72 and 74%, respectively). In contrast, far fewer prisons and GUM clinics that responded reported not screening for HCV (22 and 8%, respectively). Organisations that do not currently screen were asked if screening had been considered within their organisations, and most reported that it had not been considered (HAs 70%, prisons 89%, drug services 85% and GUM clinics 92%).

Organisations that do not screen were asked to indicate when the decision was made not to screen for HCV in their organisation. No responses were obtained from prisons and drug services. Two GUM clinics responded and reported that the decision was made in the year 2000. HAs most often reported that the decision was continual (20%), made in the year 2000 (20%) or prior to 1998 (20%).

Organisations that had actively decided not to screen were asked about influences on the decision on a 4-point scale from very influential (1) to not influential (4). No responses were obtained from prisons. The strongest influences on HAs were professionals and national and regional policy. Among drug services, the public and patients, along with regional policy, were the most influential. The most influential group on GUM clinic respondents were professionals.

Summary of the results of the diffusion study

- Screening for HCV is currently offered in a higher proportion of GUM clinics and prisons than drug services. HAs may not be fully aware of the extent of screening locally, which may suggest a lack of strategic overview of screening and imply that the initiating of screening may not have been considered across healthcare communities.
- A wide range of eligibility criteria for screening are used, with many organisations screening only those considered to be at increased risk of infection.
- A range of screening tests were reported, although ELISA followed by PCR is the most common combination.
- In many cases, organisations that conduct screening are not closely associated with those who consider treatment, and this may mean that people are screened who would not be considered for treatment. Alternative reasons for screening under these circumstances are not known.
- Treatment for HCV is widely, although not universally, available. Use of pegylated interferon in combination therapy appears limited and this treatment has not yet been assessed by NICE.

Cost-effectiveness model

A range of sources for estimates were used in the screening model. These are described in the

following section and summarised on page 38. Alternative values in extensive one-way sensitivity analyses were explored, described briefly in this section and detailed on page 40.

The epidemiology of HCV and values used in the model were described in the background chapter. The following subsections describe the choice of values for the model in each of the elements of the model.

Screening test performances (ELISA and PCR)

A screening test sequence of ELISA followed by PCR was assumed in positive cases, which the expert advisory group and diffusion study reported as the most common practice in the UK. This combination was also favoured in a French modelling study by Rotily and colleagues[86] (see the Existing economic evaluations of screening programmes section above). The use of PCR alone in sensitivity analyses was explored.

ELISA

A recent, good-quality systematic review and meta-analysis of the effectiveness of serological tests for HCV, including third-generation ELISA, was used as the source of estimates for the technical performance (sensitivity and specificity) of screening tests[101] (for methodological details see appendix 3). The values for the chronic liver disease subgroup were used in the screening model: 97.2% specificity (95% CI, 92 to 99) and 100% sensitivity. The current population of IDUs is different from those with chronic liver disease, thus introducing the possibility of spectrum bias (i.e. that the effectiveness of the test may be different when used in people with less severe disease). This issue was explored in sensitivity analyses by using lower specificities for ELISA.

PCR

Use of PCR to confirm presence of viral RNA is standard practice across Britain. PCR is also used to inform individual prognosis by determining genotype. The sensitivity and specificity of the PCR test are well established. Estimates for the sensitivity and specificity were obtained from one of the manufacturers of PCR test kits – Roche Diagnostics Ltd.[102] Results were 100% for sensitivity and specificity when tested against a sample of plasma (provided as a standard by the WHO) known to be HCV positive (n = 181). The figure of 100% was used in the economic model as the base-case estimate. When testing the PCR test against a known sample of serum (rather than plasma) in 897 cases, the sensitivity was 99.8% and the specificity was 99.3%. These figures were used in sensitivity analyses.

Diagnostic and staging test: liver biopsy

Patients with HCV undergo liver biopsy to assess prognosis (grading and staging of liver disease) or to decide on antiviral therapy.[103] It was assumed that all patients would require a liver biopsy to inform treatment eligibility (restricted to those with moderate severity disease).

Histopathology requires some subjective judgement in order to classify the individual pattern of pathological change being observed. There is, therefore, some scope for misclassification inherent in the process. The potential for misclassification was not explored in the model as it was assumed that the misclassification was likely to be random across a large population.

A literature search was conducted to estimate the probability and types of harm that might be expected from liver biopsy. Two studies were considered particularly relevant on the basis of recent publication (reflecting current practice) and large study size. One was a nationwide case series study from France investigating 2084 liver biopsies.[103] The other was a literature review including nine studies on 98,445 patients.[104] On the advice of the expert advisory group, ultrasound-guided biopsy was not considered separately.

The French case series study[103] was prospective but did not clearly include consecutive patients and relied on self-reports by medical officers, and may, therefore, have under-estimated adverse events. It used an unclear and narrow search strategy and relevant studies may, therefore, have been missed. Clear inclusion and exclusion criteria were not stated and the validity of included studies was not assessed. The homogeneity of results was not assessed and results were not pooled using appropriate methods (they were simply added together).

Table 11 summarises the main types of complications arising from liver biopsy and the rates from the literature review and case series study. The overall mortality rate in the systematic review was 0.03%[104] and this formed the base-case estimate in the economic analysis, justified by being an overview including a large number of patients and reflecting recent practice. No deaths were reported in the case series study[103] and this figure was incorporated in sensitivity analyses.

TABLE 11 *Rates and types of complications arising from liver biopsy*

Study	Number of patients	Type of biopsy	Study design	Adverse events	Severe adverse events (*n* (%))
Literature review[104]					
Gayral *et al.*, 1979	2,346	Laparoscopy, percutaneous surgery	Retrospective	Bleeding	11 (0.47%, 95% CI, 0.23 to 0.84)
Lebrec *et al.*, 1982	932	Transvenous	Retrospective	Bleeding	1 (0.11%, 95% CI, 0.03 to 0.60)
Piccinino *et al.*, 1986	68,276	Intercostal	Retrospective	Bleeding, pneumothorax, biliary peritonitis	137 (0.2%, 95% CI, 0.17 to 0.24)
McGill *et al.*, 1990	9,212	Percutaneous	Retrospective	Bleeding	22 (0.24%, 95% CI, 0.15 to 0.36)
Maharaj *et al.*, 1992	2,646	Percutaneous	Prospective	Bleeding, pneumothorax, biliary peritonitis, pain	63 (2.38%, 95% CI, 1.8 to 3.0)
Van Thiel *et al.*, 1993	12,750	Percutaneous (at a transplant centre)	Retrospective	'Major complications'	26 (0.20%, 95% CI, 0.13 to 0.30)
Janes *et al.*, 1993	405	Percutaneous (as outpatients)	Retrospective	Admissions	13 (3.21%, 95% CI, 1.7 to 3.4)
Gilmore *et al.*, 1995	1,500	Percutaneous	Retrospective	Bleeding	26 (1.73%, 95% CI, 1.1 to 2.5)
Vivas *et al.*, 1998	378	Percutaneous	Prospective	Admissions and bleeding	7 (1.85%, 95% CI, 0.7 to 3.8)
Total	98,445				306 (0.31%, 95% CI, 0.28 to 0.35)
Case series[103]					
Cadranel *et al.*, 2000	2,084	Percutaneous	Prospective	Vaso-vagal, haemoperitoneum, biliary peritonitis, pneumothorax, punctures	12 (0.58%)

The total number of complications (excluding death) from the systematic review[104] was 306 from a total of 98,445 liver biopsies performed (0.31%). The French case series study reported 12 complications from a total of 2084 biopsies performed (0.58%).[103]

In the CEA, the QALY reductions associated with complications resulting from biopsy were estimated, including deaths and costs associated with hospital admissions. Of complications, 7% were assumed to be treated on an inpatient basis with 93% treated as day cases, as reported in two of the studies within the systematic review by Poynard and colleagues.[104] The average length of inpatient stay was estimated to be 1 day.

Acceptance and adherence at each stage of the screening programme

Eight studies were identified that provided information regarding acceptance of screening and adherence to further testing and treatment. All studies were of drug-using populations. These estimates of adherence were also applied to the GUM clinic model.

Serfaty and colleagues[79] conducted a prospective study in a UK drug and alcohol clinic. During the study period, 1728 patients attended the clinic, of which 202 were considered at risk of HCV. The screening acceptance rates were reported along with attendance rates. The study also reported the number of patients who received liver biopsies and those who followed through to treatment.

Smyth and colleagues designed an HCV assessment algorithm in an Irish outpatient addiction treatment clinic.[105] They specifically studied IDUs and assessed screening acceptance and attendance rates. The study followed 138 consecutive IDUs who had presented to the clinic for the first time.

Jowett and colleagues[106] retrospectively studied 253 patients with injecting drug use as their main risk factor who presented to a regional hospital liver unit in the UK. The study used a liver biopsy-based treatment algorithm and reported the number of patients who tested positive to the PCR test, how many went on to have a liver biopsy and the results of staging of liver disease. The study also reported the number of missed appointments.

Foster and colleagues conducted a retrospective audit of the management of 255 HCV patients attending a specialist liver unit at a London teaching hospital.[70] The audit reported attendance, outcome, adherence to treatment and response to interferon-α monotherapy.

The remaining four studies identified on adherence were not used to inform the economic model because they were judged to be less applicable to the UK population. The first was conducted in a French HIV testing centre.[92] The second described screening in a USA health maintenance organisation,[89] the third was an Australian survey of young IDUs[107] and the fourth was a French study among GPs.[108]

The ideal study design of adherence, for the purpose of informing a screening model, would involve consecutive enrolment and prospective follow-up of people identified through screening in the settings of interest in the UK. Only the study by Serfaty and colleagues[79] fulfilled these criteria, but was restricted to IDUs. The study by Smyth and colleagues[105] was conducted in Ireland and also restricted to IDUs, but otherwise fulfilled the criteria. The study by Jowett and colleagues[106] was also useful, although it was hospital based.

The proportion of those eligible for screening who accepted the ELISA test was found to be 49% in the study by Serfaty and colleagues.[79] The proportion of people positive with the ELISA test who also accepted the PCR test was estimated as 100% based on clinician estimates. The study by Jowett and colleagues reported that 77% of those positive to both tests accepted liver biopsy, and 50% of patients eligible for treatment accepted treatment in the same study.[106]

Sensitivity analyses were conducted using alternative estimates from the studies described above.

Effectiveness of treatment for HCV

The assessment conducted by Shepherd and colleagues at the Southampton Health Technology Assessment Centre on the cost-effectiveness of combination therapy with interferon and ribavirin[78] formed the basis for the treatment element of the screening programme model. The transition probabilities between health states used in the model by Shepherd and colleagues are shown in *Table 12*.[109–115] A literature search was conducted for evidence on combination therapy published since completion of the Shepherd and colleagues review in 2000. An additional meta-analysis and a systematic review were found (see appendix 5 for details). Neither provided relevant additional data. The Shepherd and colleagues model was, therefore, used as the treatment element in our model, employing estimates for sustained viral response as shown in *Table 13*.

Pegylated interferon is currently licensed, although no clear national policy has been established on its use. The addition of a polyethyleneglycol molecule to interferon produces a molecule with a longer half-life and more favourable pharmacokinetics.[116,117] These characteristics permit a once per week injection compared to three times per week for non-pegylated interferon-α.

For illustration, the use of pegylated interferon for treatment following screening was modelled, using response rates reported in trials identified by a search carried out for this assessment (appendix 5 gives further details). A sustained viral response on pegylated interferon of 54% was assumed based on the results of the study by Manns and colleagues,[116] and it was also assumed that 100% of patients would use pegylated interferon.

Costs

Staff costs

The costs of nurse and medical staff time to assess eligibility and provide counselling before and after screening tests were calculated by applying wage costs to estimates of time taken for counselling. The times taken to assess and counsel individuals prior to screening and for reporting of results were obtained from the survey of current practice in HCV screening (see the Study of current practice in HCV screening (diffusion study) section above). Additional estimates were obtained from the

TABLE 12 *Treatment assumptions used in the economic model*

Assumptions	Value	Source
Clinical assumptions		
Progression to cirrhosis/annum from HCV	1%	Based on 20% progression over midpoint of 15 years converted to annual rate[109]
Progression to each of: ascites, variceal bleeds and hepatic encephalopathy from cirrhosis	1.6% (each)	Clinical consensus
Annual death rate from hepatic encephalopathy, ascites and variceal bleeds	75%	Clinical consensus
Percentage requiring transplant from complex cirrhosis states	1%	Clinical consensus
Remaining in cirrhotic state without complications	93.8%	Clinical consensus
Progression to HCC/annum from cirrhosis	1.4%	Based on Di Bisceglie, 1998[109]
Death rate/annum following HCC diagnosis	80%	Cancer registry (Web of Science)
Age at diagnosis	32 years	Based on Serfaty *et al.*, 1997[79]
Life expectancy in absence of HCV at diagnosis	30 years	Clinical estimate
Probability of successful transplant (it was assumed that patients did not re-enter the model after transplant)	90%	Clinical consensus
Probability of requiring a second transplant	10%	Clinical consensus
Death rate associated with liver transplant in first year	16%	Young *et al.*, 2000[110] (recent UK study)
Death rate associated with liver transplant in second and subsequent years	3.5%	Young *et al.*, 2000[110] (recent UK study)
Adherence to treatment once initiated	100%	Based on approximately 95% compliance rate[111]
Economic assumptions		
Cost of attendance at general practice	£17	Unit cost from Netten *et al.*, 2001[112]
Average cost of outpatient visit to general medicine	£74	Scottish Health Service Costs, 2000
Average cost/inpatient day in general medical ward	£206	Scottish Health Service Costs, 1999/2000 (general medical case of 5.4 days costs £1112)
Monthly (4-week) cost of ribavirin	£543	Average cost for 1000–1200 mg for a 4-week cycle (£494.00 and £592.80, respectively)[113]
Monthly (4-week) cost of interferon-α 2b	£194	Based on 3 mega units dose three times per week for 4 weeks[113]
Resource costs		
Annual average cost associated with HCC based on 60 inpatient days in general medicine	£13,320	Duration of stay based on clinical opinion
Annual average cost associated with cirrhosis based on three outpatient visits and three GP visits	£273	Frequency of visits based on clinical opinion
Annual average cost associated with chronic HCV infection	£108	Based on one outpatient attendance and two GP visits (clinical opinion)
Annual average cost associated with ascites based on 49 inpatient days in general medicine	£10,878	Duration of stay based on clinical opinion
Annual average cost associated with hepatic encephalopathy based on 49 inpatient days in general medicine	£10,878	Duration of stay based on clinical opinion
Annual average cost associated with variceal bleeds based on 14 inpatient days in general medicine	£3,108	Duration of stay based on clinical opinion
Cost of liver transplant and follow-up care	£46,551	National contract cost
Discount rate for costs	6%	Her Majesty's Treasury discount rate
Discount rate for benefits	1.5%	Her Majesty's Treasury discount rate

continued

***TABLE 12* contd** *Treatment assumptions used in the economic model*

Assumptions	Value	Source
Utilities		
Liver biopsy with severe complications	0.2	Clinician estimate. No available literature
Side-effects of treatment	0.5	Cotler *et al.*, 2001.[114] Most applicable population: consecutive HCV patients, visual analogue scale
Drug treatment (no side-effects)	0.89	Cotler *et al.*, 2001.[114] Most applicable population: consecutive HCV patients, visual analogue scale
Successful drug treatment, i.e. utility following successful response to treatment	0.95	Arbitrary
Chronic hepatitis	0.89	Cotler *et al.*, 2001.[114] Most applicable population: consecutive HCV patients, visual analogue scale
Cirrhosis	0.44	Cotler *et al.*, 2001.[114] Most applicable population: consecutive HCV patients, visual analogue scale
Ascites	0.35	Bennett *et al.*, 1997.[115] Only available estimate: physicians, time trade-off
Hepatic encephalopathy	0.30	Bennett *et al.*, 1997.[115] Only available estimate: physicians, time trade-off
Variceal bleeds	0.28	Bennett *et al.*, 1997.[115] Only available estimate: physicians, time trade-off
Liver transplant in first year	0.5	Bennett *et al.*, 1997.[115] Only available estimate: physicians, time trade-off
Liver transplant in second and subsequent years	0.9	Arbitary
HCC	0.10	Bennett *et al.*, 1997.[115] Only available estimate: physicians, time trade-off
Follow-up for those not screened		
Additional outpatient visit for those who are current IDUs	0	Clinician estimate. Only available evidence, reflects current practice
Additional outpatient visit for those who refuse ELISA test	0	Clinician estimate. Only available evidence, reflects current practice
Additional outpatient visit for those who are ELISA negative	0	Clinician estimate. Only available evidence, reflects current practice
Additional outpatient visit for those who are ELISA positive and PCR negative	1	Clinician estimate. Only available evidence, reflects current practice
Additional PCR tests for those who are ELISA positive and PCR negative	2	Clinician estimate. Only available evidence, reflects current practice
Additional outpatient visits for those who refuse biopsy	1	Clinician estimate. Only available evidence, reflects current practice
Additional outpatient visits/year for those with moderate disease who refuse treatment	1.5	Clinician estimate. Only available evidence, reflects current practice
Additional outpatient visits/year for those with mild disease	1.5	Clinician estimate. Only available evidence, reflects current practice
Additional outpatient visits for those with severe disease	3	Clinician estimate. Only available evidence, reflects current practice
Lead time until those with moderate disease who refused treatment present with symptoms	2 years	Clinician estimate. Only available evidence, reflects current practice
Lead time until those with mild disease present with symptoms	5 years	Clinician estimate. Only available evidence, reflects current practice

continued

***TABLE 12* contd** *Treatment assumptions used in the economic model*

Assumptions	Value	Source
***Follow-up for those not screened* contd**		
Lead time until those with severe disease present with symptoms	6 months	Clinician estimate. Only available evidence, reflects current practice
Cost of outpatient visit	£74	<http://www.show.scot.nhs.uk/isd/Scottish_Health_Statistics/subject/Costs/2000/Costs2000.pdf>. Accepted estimate for outpatient visits in the UK
Attendance rate at outpatient visits	100%	Clinician estimate. Only available evidence, reflects current practice

TABLE 13 *Virological response rates to combination therapy*

Patients	Sustained virological response rates to combination therapy
First-line therapy with interferon (24 weeks)	33% (95% CI, 29 to 37)
First-line therapy with interferon (48 weeks)	41% (95% CI, 36 to 45)

external advisory group. The time spent on counselling was varied in sensitivity analyses.

The diffusion survey was also used to estimate the ratio of nurses to doctors that assess patients and their grades. In the survey responses from GUM clinics that screen for HCV, 93 of 123 organisations reported that doctors conduct screening and 60 of 123 reported that nurses conduct screening. In the survey responses from drug services that screen for HCV, 12 of 18 reported that doctors conduct screening and 11 of 18 reported that nurses conduct screening. In some clinics, screening was conducted by both doctors and nurses. The extent to which counselling was performed by doctors versus nurses and their grades were varied in sensitivity analyses.

The survey also asked if organisations counselled patients at the time they were given their test result. Almost all GUM clinics reported that they provided counselling and this was performed by doctors in 44% and nurses in 34%. Counselling was provided by 8% of drug services, and this was provided by doctors in 43% and nurses in 71% (some drug services indicated that counselling was provided by both doctors and nurses). For the economic model, it was assumed that 50% of screening and 50% of counselling was performed by doctors. This was varied in sensitivity analyses.

Nurses conducting counselling were reported as being at grades F to H. Current salary estimates were obtained directly from the Royal College of Nursing. Most doctors conducting counselling were most often reported to be Senior House Officers and salary data were obtained from the British Medical Association. Hourly wage rates were calculated on the assumption of 4 weeks annual leave per year, 37.5 working hours per week and 15% on-costs. For both nurses and doctors, the middle of the appropriate salary range was used as the base-case estimate. For medical officers the middle of the next highest salary range (Specialist Registrar) was used in sensitivity analyses. For nurses the maximum wage for the salary range (grade H5) was used in sensitivity analyses. *Table 14* shows the calculation of costs of nursing and medical time.

Screening tests

Costs for ELISA and PCR tests were obtained from the finance departments of three local hospitals: a District General Hospital, a teaching hospital and a subregional tertiary centre (Exeter, Bristol and Plymouth). Estimates represented the costs that the hospitals charge the NHS for tests conducted on public sector patients. These charges incorporated laboratory costs for test processing and included overhead costs. The figure from Bristol Public Health Laboratory was used in the base-case analysis and the minimum and maximum values were included in sensitivity analyses.

Liver biopsy

The base-case estimate for the cost of a liver biopsy was £279 for a day case and £741 for an inpatient case, obtained from NHS Reference Costs (code G17).[118] It was assumed that 7% of

patients would have biopsy carried out as an inpatient procedure (see above), with the rest as day cases. An alternative figure for a day-case liver biopsy could be the Extra Contractual Referral cost for an investigation of HCV disease of £416 obtained from the Southampton University Hospitals Trust. While this estimate is specific to HCV, it is only one estimate from one hospital trust and is outdated. This figure was, therefore, only used in sensitivity analyses.

Treatment costs

The sources of costs for combination interferon-α therapy were as described in the assessment carried out by Shepherd and colleagues.[78] The cost of pegylated interferon was obtained from the *British National Formulary*, September 2001.[113] The costs of pegylated interferon were £810 per 4 weeks or £202.50 per week. This was based on a patient with an average weight of 65–80 kg and a dose of 1.5 µg/kg/week. The cost of ribavirin was based on an 800 mg dose: £395.20.

Utilities

Five articles were identified that estimated the utilities of health states of chronic liver disease. Two were excluded as they were based on chronic liver disease in general[72] and treatment in patients who were interferon non-responders.[119] The other three studies estimated the utilities for mild, moderate and severe symptoms of chronic HCV. All of the studies were conducted in the USA.

Two studies used physicians to value health states on visual analogue scales with zero representing death and ten (or 100) representing health without HCV.[63,115] Another study asked both patients and their physicians to rate health states on a scale with zero representing death and 100% representing health without HCV.[114] The results of these studies are summarised in *Table 15*.

When selecting the most appropriate base-case estimate for utilities, those generated by patients were preferred to those generated by physicians. The time trade-off technique was preferred over the visual analogue scale method for eliciting values. The study by Patil and colleagues[63] was the least preferred estimate on the basis of participants (physicians) and method (visual analogue scale). The study by Bennett and colleagues[115] used time trade-off in physicians. The study by Cotler and colleagues[114] was conducted in patients. Data from the study by Cotler and colleagues[120] was, therefore, used where possible.

Bennett and colleagues published the only estimates specifically for the health states associated with decompensated cirrhosis: liver transplantation, ascites, hepatic encephalopathy, variceal bleeding and HCC.[115] The sensitivity analyses included utilities from the Cotler and colleagues study[114] assuming 'severe symptoms' for all decompensated cirrhosis states.

Summary of screening assumptions

Table 16 summarises the base-case screening assumptions included in the economic model.[1,42,54,78,79,101102,106,120]

Results of the CUA

Using the base-case assumptions described in *Tables 13* and *15*, the results of the CUA and summary measures of the screening and treatment programmes are outlined in *Table 17*. In the case of GUM clinics, it was assumed that all people presenting were eligible for screening. In drug services, it was assumed that only people who were not current injectors of drugs would be considered eligible.

Results with pegylated interferon

The results when using the costs and response rates for pegylated interferon are presented in *Table 18*. All other assumptions remained the same. The lower estimates of cost–utility were driven by the higher response rates and the lower dose (and, therefore, cost) of ribavirin. Pegylated interferon is more expensive than conventional interferon.

TABLE 14 *Calculation of costs of assessing eligibility and counselling*

	Assessing eligibility		Counselling prior to ELISA		Counselling at time of test result	
	Doctor	Nurse	Doctor	Nurse	Doctor	Nurse
Proportion	50%	50%	50%	50%	50%	50%
Time taken (minutes)	1	1	30	30	25	25
Wage rate/hour	£19.38	£17.92	£19.38	£17.92	£19.38	£17.92
Cost/patient	£0.31		£9.33		£7.77	

TABLE 15 *Studies reporting utilities for health states with HCV*

Study	Sample size	Type of participant	Method of estimating utilities	HCV health stated	Utilities
Patil *et al.*, 2001[63]	113	Convenience sample of USA physicians	Written questionnaire. Health states valued on a visual analogue scale ranging from 0 (death) to 100% (health without HCV)	No symptoms, no cirrhosis	0.88
				Mild symptoms, no cirrhosis	0.66
				Moderate symptoms, no cirrhosis	0.49
				Mild symptoms, cirrhosis	0.40
				Severe symptoms, cirrhosis	0.18
				Life with side-effects of antiviral therapy	0.47
Bennett *et al.*, 1997[115]	Not stated	Not stated	A panel of hepatologists was asked to use linear scaling and time trade-off methods with 0 representing death and 10 perfect health	Mild chronic hepatitis	0.82
				Moderate chronic hepatitis	0.78
				Compensated cirrhosis	0.70
				Liver transplantation in first year	0.50
				Liver transplantation after first year	0.70
				Variceal bleeds	0.28
				Hepatic encephalopathy	0.30
				HCC	0.10
Cotler *et al.*, 2001[114]	50 patients and five physicians	Consecutive patients with HCV and hepatologists responsible for the patients	Written questionnaire. Health states rated on a visual analogue scale ranging from 0 (death) to 100% (health without HCV)	HCV no symptoms, no cirrhosis by patients	0.89
				HCV no symptoms, no cirrhosis by physicians	0.95
				HCV mild symptoms, no cirrhosis by patients	0.71
				HCV mild symptoms, no cirrhosis by physicians	0.83
				HCV moderate symptoms, no cirrhosis by patients	0.59
				HCV moderate symptoms, no cirrhosis by physicians	0.66
				HCV mild symptoms, cirrhosis by patients	0.44
				HCV mild symptoms, cirrhosis by physicians	0.49
				HCV severe symptoms, cirrhosis by patients	0.27
				HCV severe symptoms, cirrhosis by physicians	0.20
				Side-effects of HCV treatment by patients	0.50
				Side-effects of HCV treatment by physicians	0.50

Sensitivity analyses

Systematic variation of base-case estimates

A full description of the assumptions varied, the values used and justifications made are presented in *Table 19*.[52,77,79,86,102,103,105,106,114,120,121] Sensitivity analyses were performed on most of the base-case estimates in the economic model. Only the key treatment assumptions were varied, as this work had already been presented in detail previously.[78] Each variable was varied independently initially. A limited number of multi-way sensitivity analyses were then performed. The key results from the sensitivity analyses are presented separately for drug services and GUM clinics.

Varying key inputs – drug services

The drug services economic model was insensitive to the following parameters:

- the proportion of the cohort who were current IDUs and, therefore, ineligible for screening
- the underlying prevalence of HCV in populations presenting to drug services
- the proportion of eligible people presenting who accepted ELISA testing
- the proportion of people who accepted PCR testing
- the sensitivity and specificity of ELISA
- the sensitivity and specificity of PCR.

The drug services model was sensitive to the proportion of HCV-positive people who accepted a liver biopsy (see *Figure 4*). The cost/QALY increased rapidly once acceptance rates fell below 30%. The drug services model was also sensitive to the proportion of people who accepted treatment for HCV, and the resulting cost/QALY increased sharply as acceptance rates fell below 40% (*Figure 5*).

The model of drug services screening and treatment was sensitive to treatment response. When treatment response decreased below 30%, the resulting cost/QALY rose dramatically (*Figure 6*). The cost/QALY became substantially lower as the treatment response rate rose above 50%.

The drug services model was also sensitive to the following parameters that have not been represented graphically (see appendix 6 for further details):

TABLE 16 *Summary of assumptions used in the economic model – sources, values and justification*

Assumptions	Base-case estimates	Source of estimate	Justification for base-case assumption
Epidemiology			
Number of people presenting to GUM clinics annually	246,636	NASSL	Large British survey with good response rate
Underlying prevalence of HCV in people presenting to GUM clinics	1.5%	Goldberg *et al.*, 2001[54]	Largest UK study, most recent publication
Number of people who have ever injected presenting to drug services annually	101,081	118,500 present to services (Department of Health, 2001[46]) and 85.3% have ever injected (Edeh *et al.*, 2000[1])	Large UK database
Underlying prevalence of HCV in people presenting to drug services	32%	Department of Health, 2000[42]	Large IVDU UK study
Screening tests			
Proportion of those presenting to services eligible for screening in GUM clinics	100%	Expert opinion	Given the large number of people who would be subjected to screening in the proposal, limited high-risk approaches were considered
Proportion of people presenting to drug services who are not current IDUs (and, therefore, eligible for screening)	61%	Edeh *et al.*, 2000[1]	Only available estimate, UK sample
ELISA sensitivity	97.2%	Colin *et al.*, 2001[101]	Systematic review and meta-analysis of good quality. Best available evidence
ELISA specificity	100%	Colin *et al.*, 2001[101]	Systematic review and meta-analysis of good quality. Best available evidence
PCR sensitivity	100%	Roche Diagnostics Ltd, 1999[102]	Well-established values, sound methodology
PCR specificity	100%	Roche Diagnostics Ltd, 1999[102]	Well-established values, sound methodology
Diagnosis			
Proportion with mild disease	46%	Foster *et al.*, 1997[120]	Only available estimate of all three stages
Proportion with moderate disease	43%	Foster *et al.*, 1997[120]	Only available estimate of all three stages
Proportion with severe disease	11%	Foster *et al.*, 1997[120]	Only available estimate of all three stages
Adherence			
Proportion of those eligible that accept the ELISA test	49%	Serfaty *et al.*, 1997[79]	Prospective UK study, drug and alcohol clinic. Best available evidence
Proportion of those who have had an ELISA test that accept a PCR test	100%	Clinician Advisory Group	No estimates from the literature were ideal and this issue is particularly dependent on the setting
Proportion of those positive to both tests who accept biopsy	77%	Jowett *et al.*, 2001[106]	UK, IDUs, larger sample size, figures presented after both tests positive. Best available evidence
Proportion with moderate disease who accept treatment	50%	Jowett *et al.*, 2001[106]	UK, IDUs, larger sample size, study had completed follow up. Best available evidence

continued

***TABLE 16* contd** *Summary of assumptions used in the economic model – sources, values and justification*

Assumptions	Base-case estimates	Source of estimate	Justification for base-case assumption
Treatment effectiveness			
All treatment assumptions	See *Table 12*	Shepherd *et al.*, 2000[78]	These treatment analyses remain the most applicable to the current setting and study question
Harms			
Complications of biopsy	0.3%	Poynard *et al.*, 2001[104]	Good-quality systematic review of nine studies. Best available evidence
Percentage of biopsy complications resulting in admissions	7%	Poynard *et al.*, 2001[104]	Good-quality systematic review of nine studies. Best available evidence
Percentage of biopsy complications resulting in mortality	0.03%	Poynard *et al.*, 2001[104]	Good-quality systematic review of nine studies. Best available evidence
Costs			
Cost of assessing eligibility (time and wages) of each person	£0.31	National Survey of Screening for HCV, 2001 (diffusion survey)	Recent national British survey of GUM and drug and alcohol clinics. Highly relevant
		British Medical Association: mid-salary for Senior House Officers. Royal College of Nursing: mid-wage rate for grades F to H	Relevant wage rates
Cost of counselling each person eligible for ELISA	£9.33	National Survey of Screening for HCV, 2001 (diffusion survey)	Recent national British survey of GUM and drug and alcohol clinics. Highly relevant
		British Medical Association mid-salary for Senior House Officers. Royal College of Nursing: mid-wage rate for grades F to H	Relevant wage rates
The cost of an ELISA test	£12.50	Public Health Laboratory Service (Bristol)	UK, recent estimate, figure includes overheads
Cost of PCR test	£60	Public Health Laboratory Service (Bristol)	UK, recent estimate, figure includes overheads
Cost of counselling each person at time of test result	£7.77	National Survey of Screening for HCV, 2001 (diffusion survey)	Recent national British survey of GUM and drug and alcohol clinics. Highly relevant
		British Medical Association: mid-salary for Senior House Officers. Royal College of Nursing: mid-wage rate for grades F to H	Relevant wage rates
Cost of liver biopsy	£279 for a day case £741 for an inpatient	NHS reference costs	Only available estimate. Grouping called "diagnostic pancreatic or biliary procedures"
Discounting			
Discount rate	1.5%	Her Majesty's Treasury	Recommended rate

TABLE 17 *Summary of CUA*

	Drug services	GUM clinics
Number that presented	101,081	246,636
Number screened (that accepted ELISA)	30,213	120,852
Number eligible (i.e. moderate disease) and accepted treatment	1,555	292
Number that responded to treatment	544	102
QALYs gained (over no screening alternative)	303	57
Costs of screening	£3,568,314	£3,878,623
Costs of follow-up	£2,106,619	£394,988
Costs of treatment (over no screening alternative)	£3,437,539	£644,535
Costs of screening sequelae* (over no screening alternative)	–£585,459	–£109,773
Cost/QALY	**£28,120**	**£84,570**
Range of cost/QALY	£11,062–278,372	£33,268–837,199
Number needed to screen (to obtain one treatment responder)	186	2,417

* *Screening sequalae refers to the costs of treating the diseases that follow HCV, such as cirrhosis, variceal bleeds, hepatic encephalopathy and HCC*

TABLE 18 *Summary of cost/QALY for pegylated interferon in combination with ribavirin*

	Drug services cost/QALY	GUM clinics cost/QALY
Pegylated interferon (1.5 µg/kg) plus ribavirin (800 mg), response rate = 54%	£14,207	£46,389

TABLE 19 *Sensitivity analyses values and sources*

Assumptions – screening spreadsheet	Value	Source
Prevalence of HCV in target population (drug services)	67–90%	Serfaty *et al*., 1997,[79] arbitrary
Prevalence of HCV in target population (GUM clinics)	50–77%	Arbitrary, Weinstock *et al*., 1993[52]
Proportion of those presenting who are eligible for screening (drug services)	40–80%	Arbitrary
Proportion of those presenting who are eligible for screening (GUM clinics)	60–90%	Arbitrary
Proportion of screening for eligibility performed by doctors	30–100%	Arbitrary, all patients at first clinic attendance are seen by a senior registrar or consultant[120]
Cost of doctor and of nurse	£19.38 and £17.92/hour	British Medical Association mid-salary for Specialist Registrars. Royal College of Nursing wage rate for grade H5 nurse
Time taken to determine eligibility	5–15 minutes	Arbitrary
Proportion of counselling prior to ELISA performed by doctors	30–70%	Arbitrary
Time taken to counsel prior to ELISA	10–60 minutes	Minimum–maximum from the National Survey of Screening for HCV (diffusion survey)
Proportion who accept ELISA testing	10–86%	Arbitrary, 86%[105]
Cost of ELISA test	£3.00–9.63/test	Royal Devon and Exeter Hospital estimate, Derriford Hospital, Plymouth estimate
ELISA worst case: sensitivity and specificity	97.8 and 91.6%	Minimum estimates from test manufacturers (Ortho Diagnostic Systems and Abbott Diagnostics)

continued

***TABLE 19* contd** *Sensitivity analyses values and sources*

Assumptions – screening spreadsheet	**Value**	**Source**
Alternate ELISA sensitivity and specificity	99.0 and 99.6%	Previous Development and Evaluation Committee report estimates[77]
Screening with PCR only	ELISA sensitivity and specificity of 100%	Rotily *et al.*, 1997[86]
Proportion of counselling at time of test result performed by doctors	0–70%	All patients offered counselling with experienced nursing sister, Foster *et al.*, 1997,[120] arbitrary
Time taken to counsel at time of test result	15–75 minutes	Minimum and maximum response from the National Survey of Screening for HCV (diffusion survey)
Proportion who accept PCR testing	79%	Acceptance by those attending clinic at least once, Jowett *et al.*, 2001[106]
Cost of PCR test	£25.00–67.20	Leal *et al.*, 1999,[77] Derriford Hospital, Plymouth estimate
PCR worst-case sensitivity and specificity	99.8 and 99.3%	Roche Diagnostics Ltd, 1999[102]
Proportion who accept biopsy	30–90%	Arbitrary
Percentage of biopsy complications treated as inpatients	2–15%	Arbitrary
Cost of inpatient treatment for biopsy complications	£416	Leal *et al.*, 1999[77]
Mortality rate from biopsy complications	0.00–0.06%	Cadranel *et al.*, 2000,[103] arbitrary
Case mix: more severe disease at liver biopsy	25% mild, 60% moderate, 15% severe	Arbitrary
Case mix: milder disease at liver biopsy	80% mild, 15% moderate, 5% severe	Foster *et al.*, 1997[120]
Acceptance for treatment	20–90%	Arbitrary
Acceptance for treatment	40%	43% of those eligible accepted treatment, Foster *et al.*, 1997[120]
Assumptions – treatment spreadsheet	**Value**	**Source**
Drug treatment utility	0.80–0.95	Arbitrary, maximum estimate, Cotler *et al.*, 2001[114]
Chronic HCV utility	0.80–0.95	Arbitrary, maximum estimate, Cotler *et al.*, 2001[114]
Utility of ascites, hepatic encephalopathy, HCC and variceal bleeds	0.27	Cotler *et al.*, 2001,[114] assuming severe symptoms
Utility of liver transplant	0.44	Cotler *et al.*, 2001,[114] assuming moderate symptoms with no cirrhosis
Successful drug treatment utility	0.9–1.0	Arbitrary
Proportion infected who develop chronic HCV	70–95%	Arbitrary
Response rate to combination therapy	5–49%	Interferon relapsers given 24 weeks of monotherapy, interferon relapsers given 24 weeks of combination therapy, Davis *et al.*, 1998,[121] interferon naive patients given 48 weeks monotherapy
Over-treatment rate	5–10%	Arbitrary
Discount rate for benefits	0–6%	Arbitrary

continued

***TABLE 19* contd** *Sensitivity analyses values and sources*

Assumptions – follow-up spreadsheet	Value	Source
Additional outpatient visits for IDUs	1	Arbitrary
Additional outpatient visits for those who are RNA negative	0–2	Arbitrary
Additional PCR for those who are RNA negative	1	Arbitrary
Additional outpatient visits for those who refuse biopsy	0–2	Arbitrary
Additional outpatient visits/year for those with moderate disease who refuse treatment	0–3	Arbitrary
Lead time to symptoms and treatment for those with moderate disease	6 months–5 years	Arbitrary
Additional outpatient visits/year for those with mild disease who refuse treatment	0–3	Arbitrary
Lead time to symptoms and treatment for those with mild disease	2–10 years	Arbitrary
Additional outpatient visits/year for those with severe disease who refuse treatment	1–5	Arbitrary
Lead time to symptoms and treatment for those with severe disease	1 month–1 year	Arbitrary
Cost of an outpatient visit	£50–100	Arbitrary
Attendance rate at follow-up	50–80%	Arbitrary

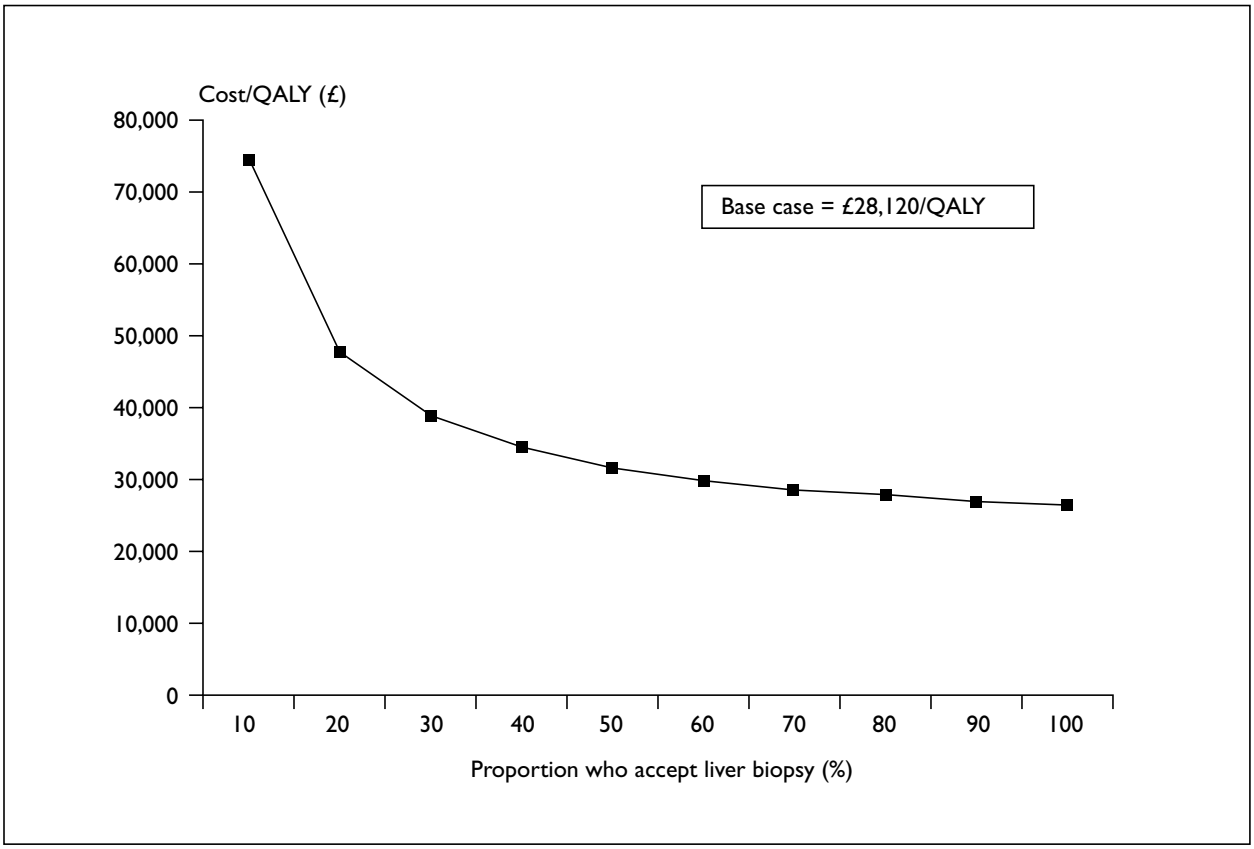

FIGURE 4 *Drug services: the resulting cost/QALY when varying the proportion of people who accept liver biopsy*

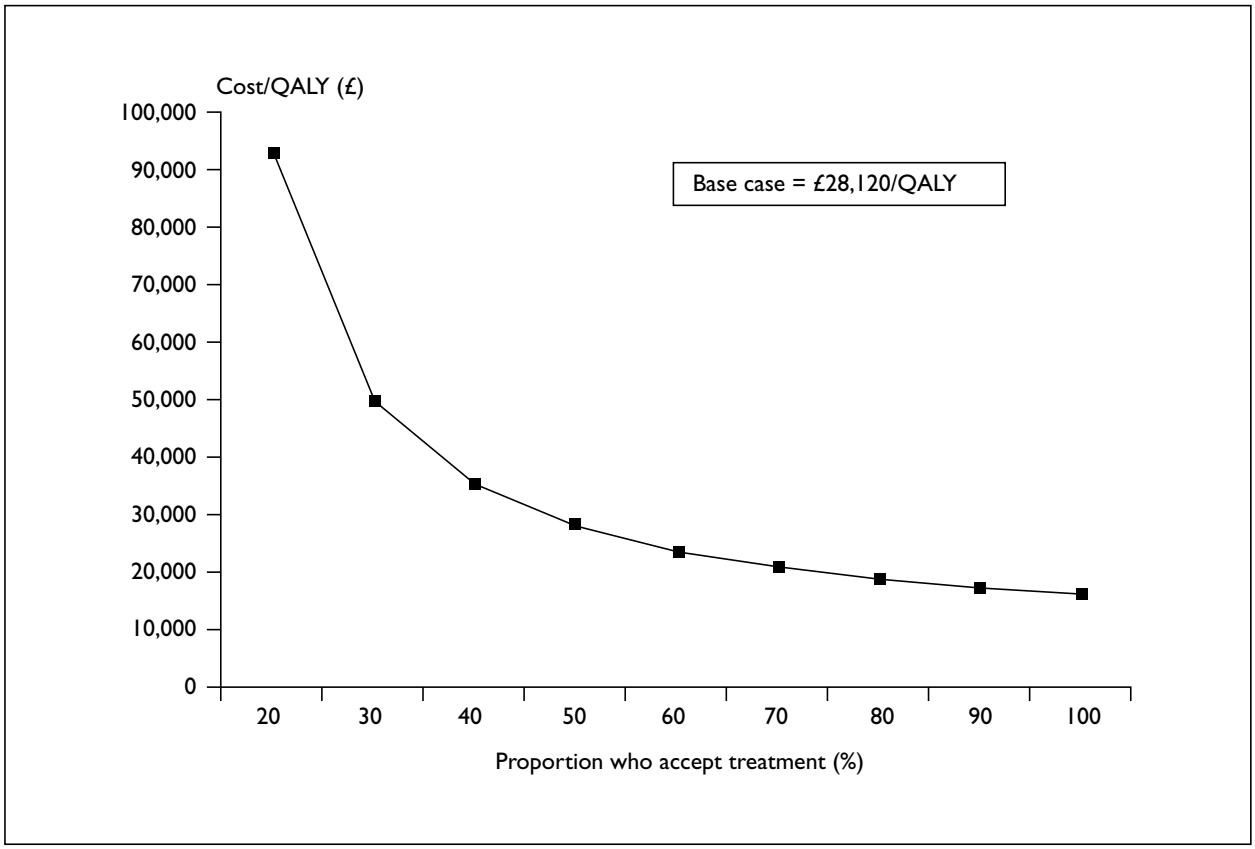

FIGURE 5 *Drug services: the resulting cost/QALY when varying the proportion of people who accept treatment*

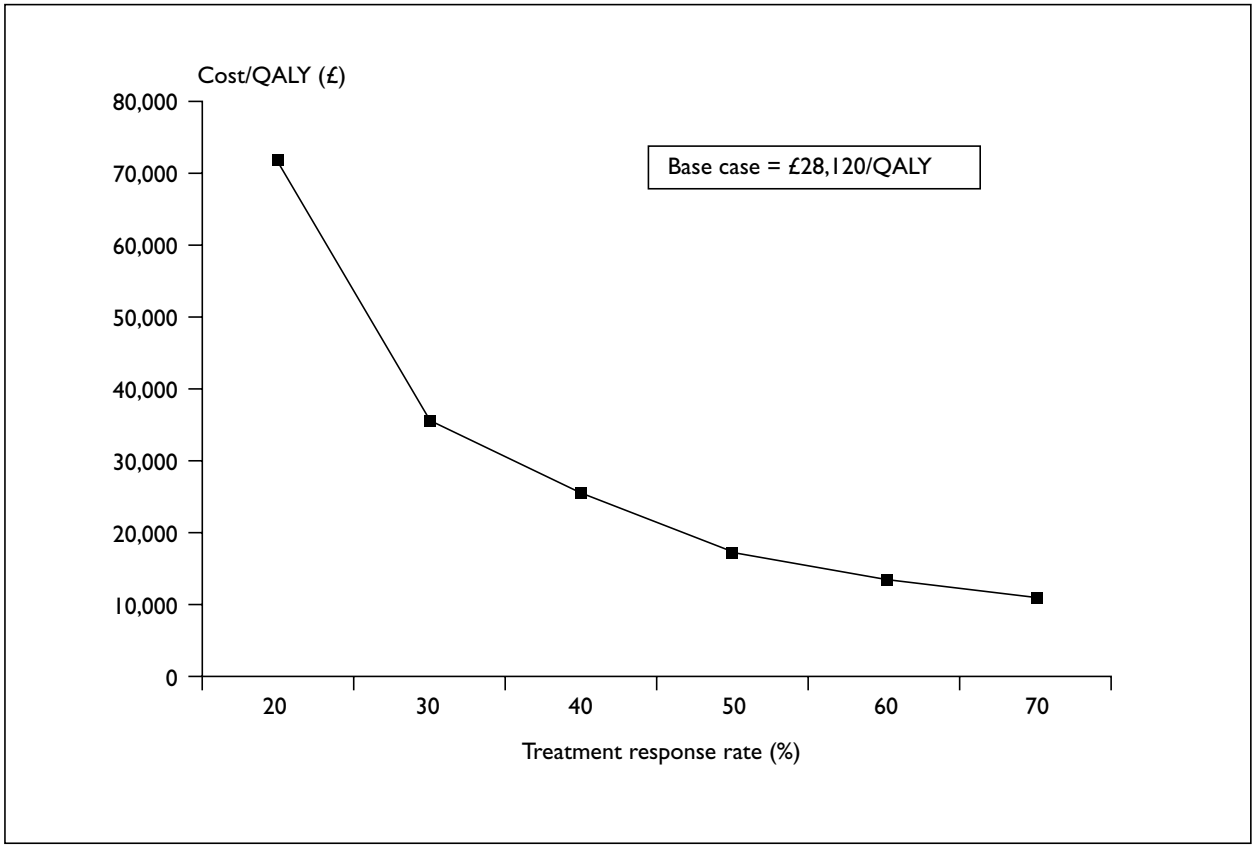

FIGURE 6 *Drug services: the resulting cost/QALY when varying the treatment response rates*

- the proportion of people eligible for treatment (i.e. those with moderate disease)
- the mortality rate associated with biopsy complications
- the assigning of current IDUs (and, therefore, ineligible for screening) to a follow-up outpatient appointment
- the utility assigned to the health state of chronic HCV
- the utility assigned to successful drug treatment.

Graphs of key variations – GUM clinics

The model for GUM clinics was, in general, more sensitive than the model for drug services. The economic model was not particularly sensitive to the following parameters:

- the proportion of people presenting to GUM clinics who were eligible for screening
- the proportion of people who accepted PCR testing
- the sensitivity and specificity of PCR.

The model was sensitive to the underlying prevalence of HCV in a population likely to present to GUM clinics. The cost/QALY increased rapidly once prevalence decreased below 3% (*Figure 7*). The model was sensitive to the proportion of people who accepted ELISA testing, especially once the acceptance rates decreased below 40% (*Figure 8*). Even when 100% of people accepted ELISA testing, the resulting cost/QALY remained £67,402. The model of GUM clinics was also sensitive to the proportion of people who accepted biopsy and the cost/QALY increased beyond £100,000 when acceptance rates fell below 70% (*Figure 9*).

In addition, the model of GUM clinics was sensitive to the proportion of people who accepted treatment (*Figure 10*) and response rates to treatment (*Figure 11*). The resulting cost/QALY rose quickly when treatment acceptance rates fell below 40% and when treatment response rates fell below 30%. The resulting cost/QALY was less than £50,000 when the treatment acceptance rate was higher than 80% and when the treatment response rate rose above 50%.

The GUM services model was also sensitive to the following parameters that have not been represented graphically (see appendix 6 for further details):

- the proportion of people eligible for treatment (i.e. those with moderate disease)
- the time taken to determine eligibility for screening (especially if the time extended beyond 15 minutes)

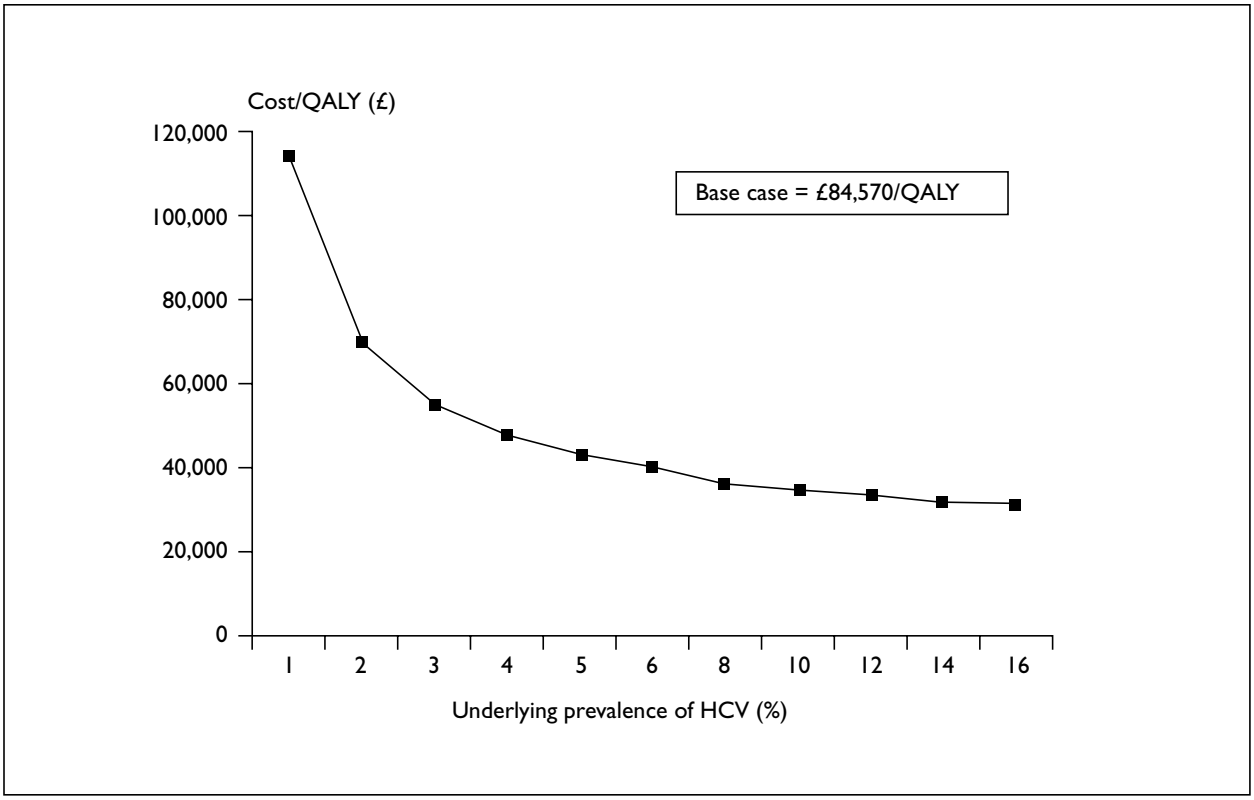

FIGURE 7 *GUM clinics: the resulting cost/QALY when varying the underlying prevalence of HCV*

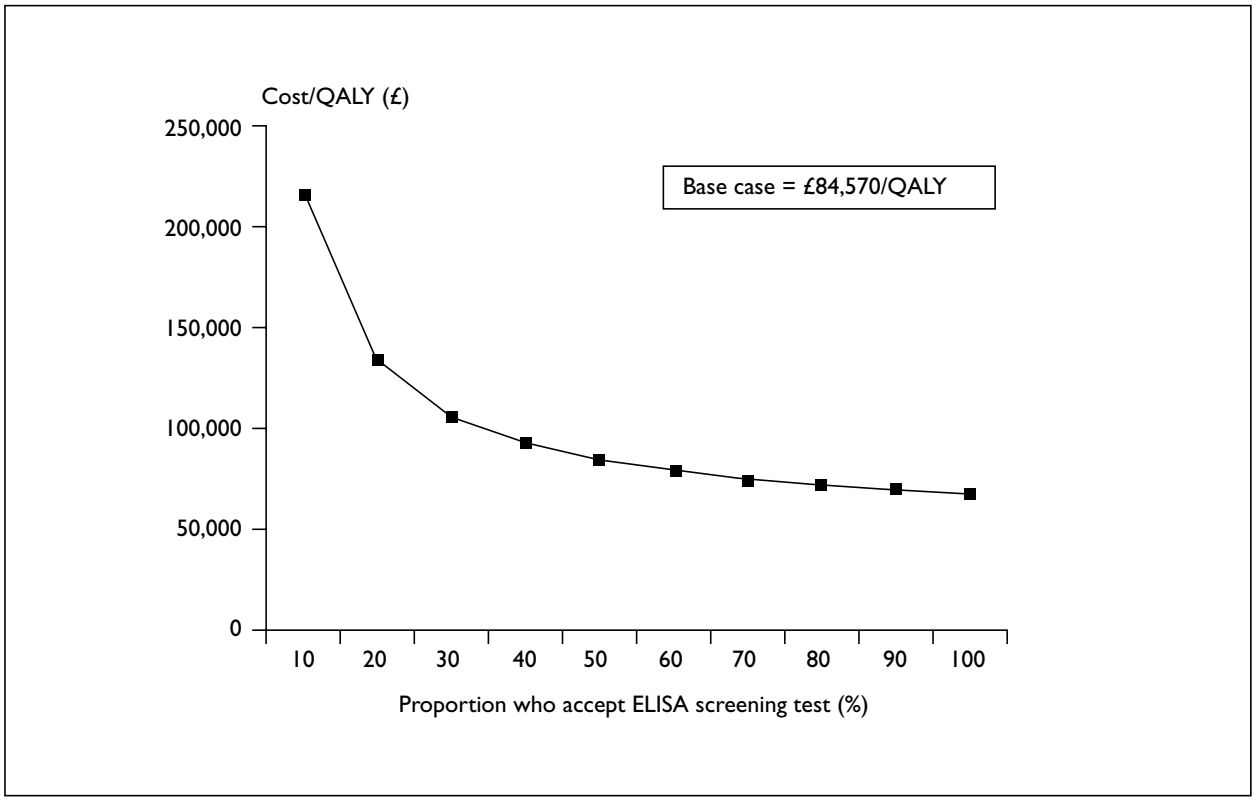

FIGURE 8 *GUM clinics: the resulting cost/QALY when varying the proportion of people who accept ELISA testing*

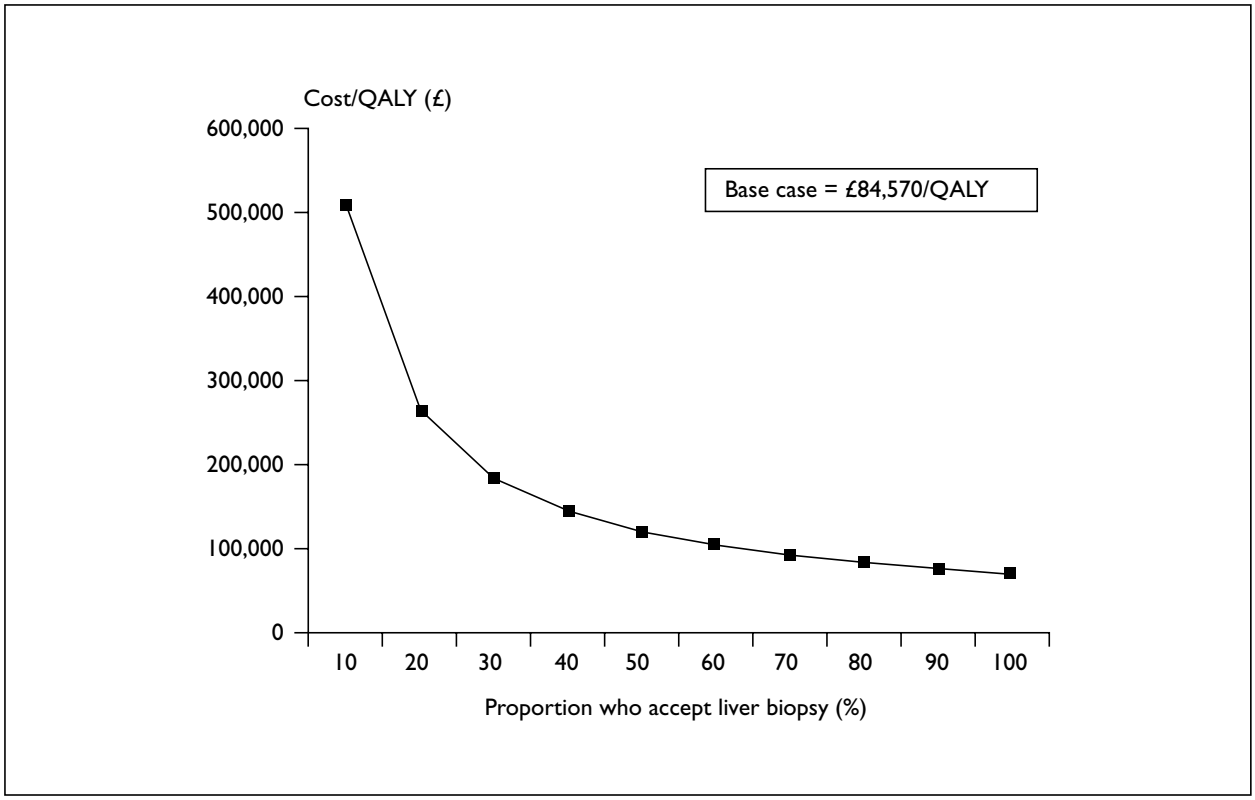

FIGURE 9 *GUM clinics: the resulting cost/QALY when varying the proportion of people who accept liver biopsy*

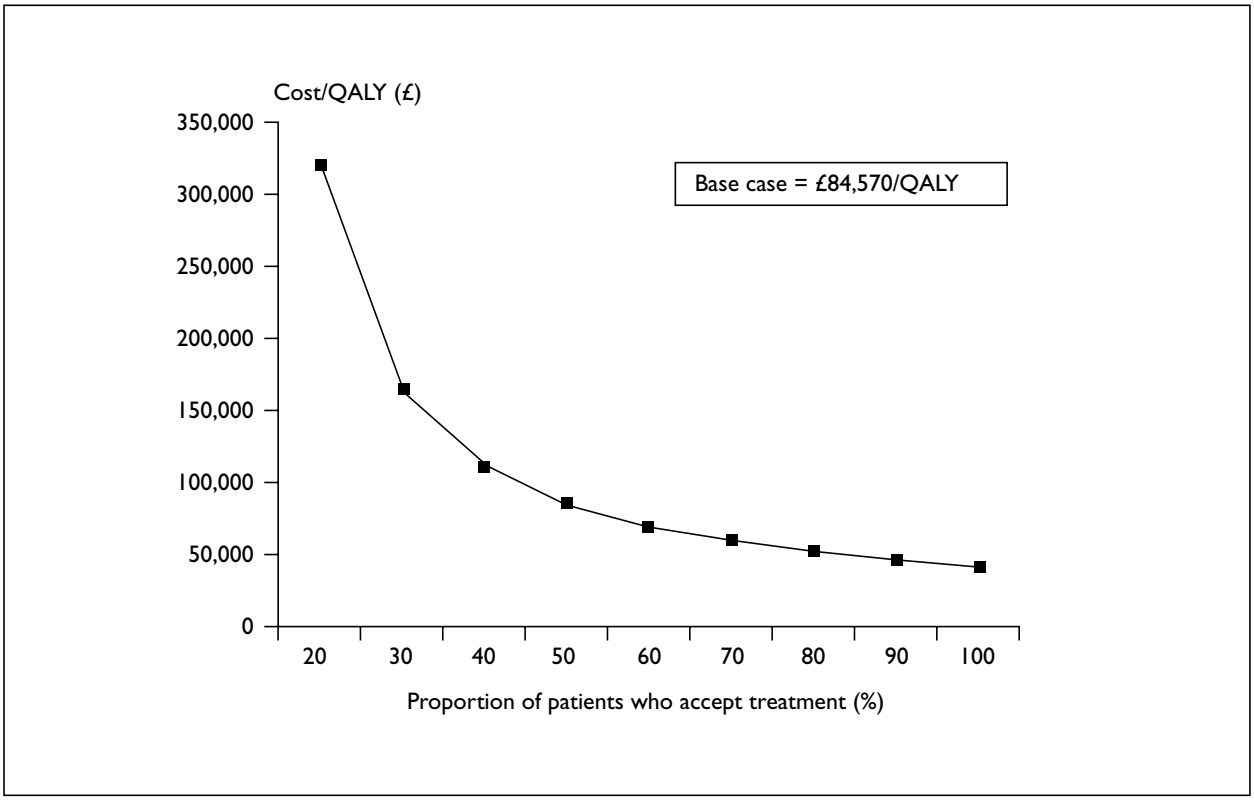

FIGURE 10 *GUM clinics: the resulting cost/QALY when varying the proportion of people who accept treatment*

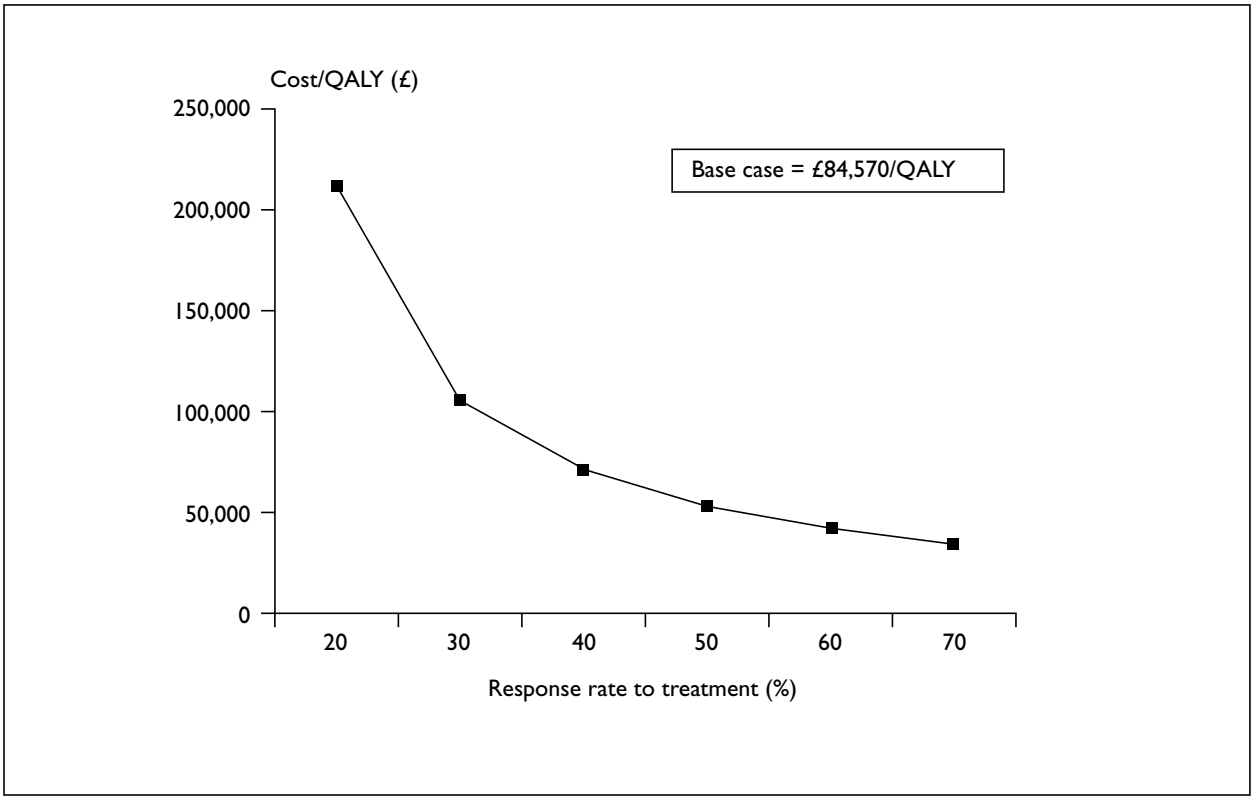

FIGURE 11 *GUM clinics: the resulting cost/QALY when varying the treatment response rates*

- the time taken to counsel a person prior to ELISA testing (especially if the time extended beyond 45 minutes)
- the ELISA test performance (sensitivity and specificity)
- the mortality rate from liver biopsy complications
- the assigning of one follow-up outpatient visit to those who tested ELISA negative
- the assigning of one follow-up visit to people who refused ELISA testing
- the utility assigned to the chronic HCV health state
- the utility assigned to successful drug treatment
- the discount rate for benefits (QALYs).

Multi-way sensitivity analyses and presentation of three GUM clinic screening scenarios

The results of the economic model showed that screening is less cost-effective in the GUM clinic setting than in drug services. The sensitivity analyses showed that as underlying prevalence of HCV increased in the GUM clinic setting the cost/QALY reduced. Three scenarios for selective screening in the GUM clinic setting were, therefore, presented.

(1) Only IVDUs are screened in GUM clinics (2.6% of all attendees).[47]
(2) Selective screening where 10% of attendees are screened based on eligibility criteria (such as intravenous drug use, sexual behaviours, contacts, etc.).
(3) Selective screening where 20% of attendees are screened based on eligibility criteria (such as intravenous drug use, sexual behaviours, contacts, etc.).

The underlying prevalence of HCV in non-current IDUs was assumed to be 48.6%.[54] The underlying prevalence of HCV in the rest of the people screened according to eligibility criteria in scenarios (2) and (3) was estimated to be 2.6% based on the findings of Tedder and colleagues who reported higher prevalence in GUM clinics than those used as the base-case estimate.[51] The results are shown in *Table 20*.

The sensitivity analyses showed that the GUM clinic results were sensitive to a number of parameters. Multi-way sensitivity analyses in which the above three scenarios were combined with variations in the following key assumptions were, therefore, conducted:

- proportion who accepted screening
- proportion who accepted treatment.

For each of the scenarios, four possible combinations of high and low estimates for these two assumptions were examined. Estimates were based on empirical data where possible. The high and low estimates shown in *Table 21* were used, and results of these multi-way sensitivity analyses are shown in *Table 22*.

TABLE 20 *Three GUM clinic screening scenarios*

Scenario	Number eligible for screening	Underlying prevalence	Cost/QALY	Total cost (in addition to no screening)
Base-case scenario	***246,636***	***1.5%***	***£84,570***	***£4,808,373***
1. Only IVDUs screened (non-current injectors)	3,912	48.6%	£27,138	£982,832
2. Selective screening of 10% who present	24,664	9.9%	£34,288	£1,530,547
3. Selective screening of 20% who present	49,327	6.2%	£39,647	£2,168,860

TABLE 21 *High and low estimates for the proportion who accept screening and accept treatment*

	High estimate	Low estimate
Proportion who accept screening	86%[106]	30%
Proportion who accept treatment	70%	30%

TABLE 22 *Multi-way sensitivity analyses for three GUM clinic screening scenarios*

Scenario	Cost/QALY	Total cost (in addition to no screening)
Base-case scenario	***£84,570***	***£4,808,373***
1. Only IVDUs screened		
High estimate for the proportion who accept screening and high estimate for the proportion who accept treatment	£20,011	£2,006,862
High estimate for the proportion who accept screening and low estimate for the proportion who accept treatment	£46,787	£1,397,230
Low estimate for the proportion who accept screening and high estimate for the proportion who accept treatment	£20,747	£719,836
Low estimate for the proportion who accept screening and low estimate for the proportion who accept treatment	£49,002	£507,174
2. Selective screening of 10% who present		
High estimate for the proportion who accept screening and high estimate for the proportion who accept treatment	£23,610	£2,933,212
High estimate for the proportion who accept screening and low estimate for the proportion who accept treatment	£57,614	£2,150,268
Low estimate for the proportion who accept screening and high estimate for the proportion who accept treatment	£27,224	£1,147,846
Low estimate for the proportion who accept screening and low estimate for the proportion who accept treatment	£68,485	£874,726
3. Selective screening of 20% who present		
High estimate for the proportion who accept screening and high estimate for the proportion who accept treatment	£26,307	£4,007,843
High estimate for the proportion who accept screening and low estimate for the proportion who accept treatment	£65,727	£3,027,205
Low estimate for the proportion who accept screening and high estimate for the proportion who accept treatment	£32,078	£1,305,262
Low estimate for the proportion who accept screening and low estimate for the proportion who accept treatment	£83,086	£1,305,262
Range	£20,011–83,086	£507,174–4,007,843

Chapter 4

Discussion and conclusions

Discussion

The assessment has addressed a range of issues in screening for HCV.

Review of existing economic evaluations

A review of existing economic evaluations revealed no more comprehensive or relevant evaluations than the study carried out for the South and West Regional Development and Evaluation Committee in 1999.[77] Studies of screening in other countries were of limited scope and/or were of very limited relevance to the UK setting.

Epidemiology of HCV

The epidemiology of HCV in the UK appears to be somewhat different from that in other countries, with some indication of lower prevalence. HCV presents a significant burden of disease, and reductions in QoL are not restricted to advanced stages of the disease.

IDUs currently constitute a large proportion of the prevalent pool of people with HCV and this is likely to increase following more effective control of the risk of iatrogenic infection. The natural history of HCV disease in this population is less well understood.

The issue of sexual transmission is particularly important in considering the appropriateness of screening in GUM clinics. We conclude that the evidence for sexual transmission as an epidemiologically important route for HCV transmission is not strong. In particular, little evidence was found to support the hypothesis that sexual transmission is associated with sexual orientation, particular sexual practices or number of sexual partners. There was evidence that the prevalence of HCV among GUM clinic attenders is not markedly higher than the general population and that prevalence in this setting is predominantly made up of people who are IDUs, and studies addressing this issue have been particularly subject to confounding.

HCV is highly prevalent among IDUs, although estimates in the UK population from the anonymous unlinked surveillance programme are lower than those reported from other studies. Volunteer surveys are prone to bias, and the higher prevalence seen in such populations may reflect people at higher risk being more likely to come forward, perhaps as a way of determining their HCV status.

Survey of current practice

The study of the diffusion of HCV screening among drug treatment services, GUM clinics and prisons showed that screening is being undertaken in many areas. This was inevitably only a snapshot and may rapidly become out of date as services continue to develop. GUM clinics are more likely to offer screening than drug services, which, given the different prevalence of HCV in these settings, may be surprising. However, this finding may reflect the fact that GUM services routinely conduct blood tests for a variety of reasons, whereas this is not routinely an aspect of the work of drug services.

Many HA respondents were unaware of screening being conducted in their areas. This may be because our survey failed to reach the most appropriate professional within HAs, although this is unlikely because the survey was addressed to Directors of Public Health, who are responsible for control of communicable disease within HA areas in England, and a good response rate was obtained.

Several factors point to a limited strategic basis for the initiation of screening in services:

- limited awareness of screening by HAs
- variation in screening policies
- evidence that those who are conducting screening are frequently unaware of eligibility for treatment in their area
- few services conducting screening, apart from prisons, were able to report when screening started.

Current changes to the organisation of the NHS may have some implications for the development and maintenance of strategic management of screening. Drug Action Teams have a role in harm reduction related to drug use and this may extend to screening for HCV. The communicable disease control function, which is currently a responsibility

of district HAs will move to the new National Infection Control and Health Protection Agency, but it is unclear whether screening for HCV will be considered as part of its remit. Primary Care Trusts will continue to have responsibility for commissioning services from the secondary care sector, including GUM clinics, although it is likely that commissioning arrangements for GUM clinics vary and may not specify screening. These complexities may mean that careful consideration of screening and achievement of a coherent approach to its value in local healthcare communities may be challenging.

It is possible that the diffusion survey failed to reach the most appropriate person in each organisation, and this is more likely for drug services than GUM clinics or prisons because the sampling frame for drug services included a wider range of types of service. This may also have accounted for the lower response rate among drug services – some services may have considered screening irrelevant, for example, tertiary treatment services or services offering only information and advice.

Although we asked for information on the number of people screened for HCV, this yielded very little robust information in any setting. Where screening is selective, as is the case in most GUM clinics and prisons, we do not know the proportion of people presenting to services who would be offered screening on the basis of perceived risk factors.

Policies on eligibility for screening vary considerably, although the main groups currently offered screening in drug services and prisons are IDUs. GUM clinics employ a wider range of eligibility criteria. The responses to the survey on this issue were less detailed than we had hoped would be obtained and suggest the need for further research. The widespread use of sexual behaviour as criteria for screening suggests that beliefs regarding the importance of this route of infection are strongly held and should be investigated further.

The diffusion survey provided limited information on screening interval. Repeat screening is the norm in GUM clinics, which may be related to the maintenance of anonymity, or misinterpretation of screening as meaning the availability of testing to service users who request it. Where the reasons for a screening interval were justified, the commonest reason related to the inability of screening to detect infection before production of an antibody response. No respondents reported policies regarding screening of people known to be antibody positive and RNA negative, or among people successfully treated in whom re-infection remains a risk.

Treatment for HCV is widely available, although we are aware from personal experience that some HAs have placed a limit on funding, which our survey did not explore. Reports of eligibility criteria for treatment varied with a substantial proportion of respondents indicating that this was a matter for the clinicians that initiate treatment. The question asked in the survey was open-ended and responses varied accordingly in detail, making it difficult to describe variation.

A sizeable minority of respondents from GUM clinics and prisons did not know whether treatment was available in their area. In these cases, there has either been an assumption of treatment availability or screening has been instituted on the basis that knowledge of HCV status is likely to be of value to infected individuals regardless of treatment availability, for example, in order to promote reduction of the risk of infection to others.

Impact of knowledge of HCV status on risk behaviours

The systematic review of the effects of knowledge of HCV status on behaviours associated with risk of virus transmission identified very little good-quality evidence. Our conclusion is that there is currently no compelling evidence to suggest that gaining knowledge of HCV status is likely to lead to behavioural changes that will reduce the risk of infection to self or others. This view is not shared by others, who believe that objective knowledge of HCV status among IDUs following counselling and screening is the way ahead, not only to accelerate the change to injecting cessation but to minimise HCV spread to their injecting counterparts,[79] and that screening is relevant to identify and change behaviour in IDUs who are HCV negative.[95] Others have commented that screening for HCV provides an opportunity to identify HBV infection and to support reducing alcohol consumption. These issues were beyond the scope of this assessment and suggest that the policy question is broader than for HCV.

In view of the limited evidence base, we cannot reject the idea that establishing knowledge about HCV status could be part of effective interventions to produce behavioural changes with positive impact on the spread of HCV. There is currently insufficient information on different interventions associated with giving information on HCV status,

for example, involvement of peer groups, methods for ongoing support or the impact of the timing of information in relation to a person's readiness to change.[122] More research into this area is needed, particularly given current interest in preventing the spread of HCV and reducing the harms of drug misuse, which may help to stimulate innovation in relevant services. We believe that policy makers should carefully consider whether the current evidence base for behavioural change is sufficient to support screening among those who would not be considered eligible for treatment.

Cost-effectiveness of screening

The cost–utility model of screening estimated that screening among IDUs would yield benefits at a cost of about £28,000/QALY. In GUM clinics, screening appeared to be less cost-effective at about £85,000/QALY. These results are higher than those reported in the previous modelling study, which reported a cost/QALY of £27,125 in GUM clinics and £10,177 for IDUs.[84] The main reason for the difference is the inclusion in the current model of an estimate of treatment in people not identified through screening, based on an assumption of infection becoming apparent 11 years later in the absence of screening.

A wide range of one-way sensitivity analyses showed that the estimates for screening in drug services appears to be more robust, although the model was sensitive to several parameters. Acceptance of biopsy was an important variable, as, at this stage, considerable costs have been incurred through screening and confirmatory testing. A reduction in the number of people considered for treatment substantially affects the overall population benefit. The estimate used in the base case came from a retrospective study of 253 IDUs in a regional liver disease treatment centre.[106] This was the largest UK study identified. Although the CIs on the proportion (77%) of HCV RNA-positive cases who attended for biopsy (70 to 83) in this study suggested that variation in biopsy adherence was unlikely to make a substantial difference to cost-effectiveness, it should be noted that this was a small study and that wider variation was shown in other studies. For example, Serfaty and colleagues[79] reported that 18 of 28 eligible patients had a biopsy (64%, 95% CI, 44 to 81). The imprecision around this estimate is consistent with an increased cost-effectiveness ratio.

Eligibility for treatment and treatment response rates were important determinants of the cost-effectiveness ratio. There may be some doubts about the effectiveness of combination therapy in different populations from those used in the clinical trials of the drugs, but it seems unlikely that treatment response rates will be so low as to make a substantial difference to the cost-effectiveness of screening. However, the uncertainty about this issue suggests a case for considering the use of registries to follow-up the treatment of people with HCV and for recording whether they were identified through screening.

The role of eligibility criteria is related to response. Where a higher proportion of people are considered eligible, cost-effectiveness is greater. However, this assumes that response rates remain constant between groups, which has not been tested.

The screening models in both IDUs and GUM clinic populations were sensitive to changes in the utility weights applied to the time spent in health states associated with chronic HCV disease. It is not surprising that these should be an important variable in the model. Unfortunately, there was considerable variation in utility estimates, which were based on, in all studies, the valuations of a small number of people. There is some reassurance in the case of HCV that people with the condition do not differ systematically from clinicians in health state valuation, but it remains a point for debate whether it should be people with HCV, their clinicians acting as proxies or the general public who provide estimates of utility.

There is potentially greater uncertainty in the cost-effectiveness of screening in GUM clinics than in IDUs presenting to drug services. Acceptance of screening in GUM clinics is a particular area of uncertainty, and is also dependent on local policies for offering screening, which vary. Where acceptance of screening is less than 40%, cost-effectiveness increases markedly. We have no information on acceptance in GUM clinics.

Overall summary of results

- Screening for HCV is carried out widely in the NHS, but there is significant variation between settings and organisations. Screening was more frequently reported in GUM clinics than drug services.
- Screening for HCV in IDUs is estimated to yield benefits over no screening at a cost of approximately £30,000/QALY. This estimate is reasonably stable in a wide range of one-way sensitivity analyses. Lower cost-effectiveness may be associated with low acceptance of liver

biopsy and treatment with combination therapy. Pegylated interferon may substantially increase the cost-effectiveness of screening, although information on the effectiveness of this new treatment is still emerging and has not been exhaustively reviewed.
- The cost-effectiveness of universal screening in GUM clinics is estimated to be about £85,000/QALY and is subject to greater uncertainty than the estimates for cost-effectiveness in IDUs, as might be expected given the much lower prevalence in this population.
- Selective screening in GUM clinics is likely to be more cost-effective than universal screening, but there is still considerable uncertainty. Only under assumptions of high acceptance of screening and/or adherence to treatment do selective screening strategies achieve levels of cost-effectiveness that might be considered to represent good value for money, in the absence of other considerations, by policy makers.
- As yet, there is no compelling evidence that gaining knowledge of HCV status produces changes in behaviour that might reduce the spread of the virus, although the evidence base is insufficient to reject the possibility that such effects exist.

Methodological strengths and weaknesses of the assessment

This assessment has several strengths over previous research into screening for HCV. It demonstrates that no relevant comprehensive evaluations of the cost-effectiveness of screening in the UK have been published since our previous work in this area.[77] The assessment includes the first systematic review of the impact of knowledge of HCV status on behavioural changes and reports the only national survey of screening for HCV in the UK.

The model of cost-effectiveness significantly improves upon previous work relevant to the UK. Our previous screening model had several methodological limitations, which were acknowledged at the time. It did not include treatment of people with HCV identified other than through screening, the natural history of HCV was based on a study that assumed a similar course to HBV infection and it allowed only for a crude method of discounting of costs and benefits. The treatment element of the model was based on interferon-α monotherapy, which has been superseded by combination therapy with interferon-α and ribavirin. The current model addressed these limitations and was based on more empirical evidence for the effects of adherence at different stages of screening and treatment.

There were, however, a number of potential weaknesses. The systematic review of the impact of knowledge of HCV status was informed by literature searches that were limited to electronic databases and contacts with experts. We may have missed some relevant studies published in journals not listed in the databases used or not identified by the search terms used. We consider this to be unlikely because reviews of the reference lists in the articles identified yielded no further references. Furthermore, the quality of studies identified was, in general, low, and publication bias was unlikely to have led to the exclusion of studies of higher quality than those identified, making it unlikely that the conclusions of the review would have been substantially altered by identification of further studies.

Overall response rates in the diffusion study were reasonable, but lower than ideal, in drug services. The sampling frames for the diffusion study, in particular that used to identify drug services, may have included services for which screening for HCV was inappropriate. It was beyond the scope of the study to conduct a preliminary assessment of the appropriateness of inclusion. The response rates for the diffusion study may, therefore, be somewhat deflated, as services for which the study appeared to be irrelevant may have been less likely to respond and could have been excluded at the outset. We consider this effect to be of limited importance.

The questionnaire used in the diffusion study had some limitations and some responses reveal ambiguity in respondents, reflecting the limited time available for piloting and refining the survey instrument.

The model of cost-effectiveness had a number of limitations, both internal (i.e. model structure) and external (i.e. the quality of evidence available to inform parameters). The usual assumptions in a Markov chain process apply – that transition between health states is independent of the time spent in preceding health states. The model is highly deterministic, that is, the transition probabilities and parameter estimates are fixed in the base case. In the base case, the model, therefore, takes very limited account of uncertainty in underlying parameters.

The model is not stratified for different ages at entry because the age distribution of people

identified through screening is unknown. If the population age distribution is skewed towards those younger than the average age of 32 assumed in the model, then the cost/QALY ratio for screening may have been under-estimated (as people would have had longer to develop complications of HCV). Conversely, if the distribution is negatively skewed, then the model may have incorporated an element of over-treatment, thereby, inflating the potential benefits of screening. It is not possible to conclude on the direction and strength of this effect.

Death rates from other causes were derived from standard life tables of Great Britain, which are likely to under-estimate the force of mortality in IDUs and, therefore, over-estimate the cost-effectiveness of screening. The number of IDUs varies within England, with London and the northwest having the highest rates. This would impact on the cost of screening programmes. Effects on cost-effectiveness depend on a range of other variables, including prevalence, acceptance and adherence, on which we have few data on geographical variation.

The model incorporated treatment for people who were not identified by screening, but did this by assuming that they were identified, on average, 11 years later than they would have been in the presence of screening. This assumption is untested and the model is sensitive to this parameter.

The quality of evidence underlying the estimates used in the model varied. Evidence for the effectiveness of treatment with combination therapy was of high quality but costing information was more limited. Sources for the costs of treating complications of HCV infection were drawn from routine NHS sources and were predominantly driven by length of hospital stay. More detailed HCV-specific costs would have enhanced the model, but were currently unavailable. We did not include the costs of psychiatric assessment in people with HCV being considered for treatment, which may be common, and did not incorporate any estimate for the psychological distress caused by misclassification of HCV status through screening. However, we believe the effects of these omissions are not likely to be significant.

Although more estimates for adherence were obtained for this model than our previous model, no evidence was available for adherence in people who were not IDUs. However, as IDUs make up the majority of people likely to be identified through screening, the effect of this assumption (which may be to under-estimate cost-effectiveness) is considered to be small. In the case of IDUs, we have linked eligibilty for screening with eligibility for treatment, in so far as people who were currently injectors would not have been considered eligible for treatment. Other criteria affecting eligibility for treatment were in clinical use (e.g. alcohol consumption, psychiatric status), which were not considered. The effect of this is to bias the model in favour of screening, as a proportion of people who, in the model, proceed to treatment, would not be treated in practice.

The model did not take into account rates of non-attendance in health services at the various stages of screening, diagnosis and treatment and, therefore, under-estimated the true cost of screening, because average outpatient clinic costs did not take into account the loss of productivity due to wastage. The sometimes chaotic lifestyles of many HCV-positive IDUs is well recognised. During 8 years of experience in a regional centre, Jowett and colleagues[106] reported the mean number of missed appointments per person at nearly three and that 747 clinic appointments were wasted through non-attendance (30% of the total).

Many of the estimates for the utilities associated with relevant health states in the model were taken from a study of American hepatologists. There is some evidence that physicians differ in their valuation of health states from other professionals, but in the case of HCV the only study that we are aware of that has examined this issue reported close congruence of views. Whether the utilities of health states used in economic evaluations should be measured by people experiencing those states, healthcare professionals acting as their proxies or by members of the general public is a point of methodological debate. Ideally, utility estimation should also take into account QoL at different ages. Estimates used in the model for all treated people were set at 0.95 and did not vary with age. Between the ages of 45 and 49, the average QALY score estimated from a population sample in the UK was 0.84, and 0.7 at the age of 82. The utility of CAH (0.89) prior to diagnosis and treatment was also important given the structure of the model. We assumed that people who were identified through screening were treated 11 years earlier than they otherwise would have been and that, following successful treatment, utility would be 0.95. The difference between pre- and post-treatment utilities was, therefore, applied to the 11-year period, and since most

people were in the chronic HCV state this utility contributed considerably to the calculation of benefits.

It was unclear whether the utility associated with chronic HCV varied between people who would have been identified through screening and those identified through symptomatic presentation. The QoL studies cited in the QoL and HCV disease section of chapter 1, which emphasise the decrements in QoL associated with chronic HCV, were mostly carried out in the context of RCTs of interferon and it was unclear whether participants were identified through screening or presented to health services with symptoms. The utility modelled for chronic HCV without cirrhosis was estimated by a group of patients, but the circumstances of their diagnoses were not reported. If the utility of CAH identified through screening was higher than we estimated and the utility following treatment lower then the benefits of screening may diminish considerably.

Implications of the assessment for the NHS

Organisational implications for the NHS

Screening is already being conducted in many GUM clinics and drug treatment services in England. It is not possible to say whether the organisational implications of screening have been considered across healthcare communities, but it seems likely that, in many places, screening was initiated by enthusiasts within services. The workload implications within screening settings may, therefore, have been absorbed within current capacity. We did not include laboratories within the diffusion survey and, therefore, cannot assess whether screening has had a marked impact on workload and capacity within that sector. Similarly, we cannot conclude on the current and potential impact of screening for HCV on secondary care and GP services. GP involvement in screening may remain confined to those with an existing interest and relationship with drug treatment services, for example, through Shared Care Monitoring Groups.

Two factors may mean that the number of people considered for screening in this assessment may increase in the future. Our assessment was based on IDUs in contact with drug services, which is a small minority of IDUs in the community.[123] Current efforts to increase provision of needle exchange programmes and supervised consumption of controlled drugs will increase the potential number of people considered for screening.[12] Drug misuse statistics show a steady increase in the number of service users.[46] If treatment is made available to IDUs who are currently injecting, as has been suggested,[124,125] the number of people who may be included in screening would increase by at least 25% over the estimates used in this report. Whether existing information on acceptability and adherence of screening would be relevant in this extended group is uncertain.

Acceptability of screening

There is some evidence to support acceptability of screening in the target populations. However, the possible absence of strategic consideration of screening in many areas suggests that the priority that should be placed on screening against other calls on NHS funding may not have been made explicit.

Management and monitoring

In the context of HCV, screening is taken to mean case finding. A more comprehensive, population-based approach to screening, as is carried out in the cancer screening programmes, would mean the compilation of registers of those eligible for screening and systems of call and recall. The feasibility of such measures may be very limited given the nature of the populations being screened, with the exception of the prison population.

Notwithstanding the issue of cost-effectiveness of screening and policy regarding its availability, current variation in awareness of and criteria for treatment eligibility suggests that policy makers may wish to consider the potential for reaching clearer consensus and supporting this with guidelines and audit.

Conclusions

It is beyond the brief of this assessment to make policy recommendations to the NHS. The purpose of the assessment is to inform the development of policy by estimating the effectiveness and cost-effectiveness of screening. Our conclusions are as follows.

The objectives of screening for HCV should be clarified. Policy makers might wish to clarify whether the primary purpose of screening is to identify infected individuals for treatment, to enable monitoring of infected individuals

regardless of eligibility for treatment, to achieve harm reduction in relation to the progression of HCV disease through reducing alcohol consumption or to influence behaviour in relation to the spread of HCV. Evidence in support of behavioural changes in relation to HCV is currently not compelling.

Screening for HCV in IDUs in contact with services is moderately cost-effective (about £30,000/QALY) and reasonably stable when explored in extensive one-way sensitivity analyses. Uncertainty around acceptability of screening and adherence to treatment and the simple nature of our model means that we recommend some caution in accepting this estimate.

Universal screening in GUM clinics is less cost-effective and subject to greater uncertainty than screening IDUs in contact with treatment services. Assessment of selective screening policies in the GUM clinic setting is restrained by scarcity of information on the epidemiology of HCV in groups other than IDUs. While selective screening may be more cost-effective and affordable than universal screening, we believe that it remains open to question whether seeking people other than IDUs for screening represents a cost-effective use of NHS resources.

Further research

Recommendations for further research

Further research in the following areas would be valuable.

- The epidemiology and long-term natural history of HCV disease in different populations, particularly those presenting to GUM clinics.
- A systematic review of the role of sexual transmission of HCV.
- Improved modelling for the cost-effectiveness of screening, based on more sophisticated methods, for example, discrete event simulation to introduce a more stochastic approach, extending the analysis beyond the prevalent round of screening and incorporating more realistic modelling of the no-screening alternative.
- Further empirical investigation into screening in different settings, including more detailed investigation of screening in GUM clinics, in particular to provide more data on acceptance and adherence within screening programmes and reasons for selection of eligibility criteria for screening.
- Development and evaluation of interventions to produce behavioural changes among IDUs in relation to HCV infection. Studies should be longitudinal, specify the intervention more clearly and measure behaviour changes more precisely and with greater power to demonstrate effects. This should include an evaluation of the information currently given to participants in screening programmes.
- Research to consider whether there are differences in effect according to specific characteristics of the population and setting for intervention, such as duration of injecting, presence of co-infection or morbidity, sex and setting in which screening is conducted.
- Monitoring of treatment response and long-term follow-up of people identified through screening.

Ongoing and unpublished research

During the course of the assessment, we have been made aware of some relevant ongoing research in this area.

- A follow-up of screening programmes in France to describe adherence and outcome is expected to be published in 2003 (Dr JC Desenclos, Paris: personal communication, October 2001).
- Dr J Roberts and colleagues at the School of Hygiene and Tropical Medicine, London are studying the costs of treating HCV disease.
- Dr P Cook and colleagues at John Moore's University, Liverpool are conducting a longitudinal study of behavioural changes following knowledge of HCV.
- A Department of Health funded study by the Public Health Laboratory Service, Bangor (Dr M Walker) into qualitative aspects of HCV screening in IDUs has been completed and final report submitted in December 2001.
- Further evidence for the effectiveness of pegylated interferon may be published during 2002 and a systematic review of this new treatment option will be required.
- Dr A Pithie at West Glasgow Hospital University NHS Trust, Glasgow received a grant from the NHS Policy Research Programme to investigate the impact of harm reduction initiatives on HCV in IDUs. It was planned that those identified as HCV negative would be followed up and offered annual re-testing. This cohort may yield useful information on effects on risk behaviour.
- The National Registry of HCV Infections is funded until 2004.

- Professor G Stimson at Imperial College, London has been funded until April 2004 by the Policy Research Programme to establish a cohort study to assess the prevalence and incidence of and risk factors for HCV infection among IDUs.
- An RCT of enhanced counselling compared to simple educational counselling in the primary prevention of HCV among IDUs is being conducted by Dr M Abou-Saleh at St George's Medical School, London (end date 3 March 2003).

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Contribution of authors

Dr Ken Stein, Senior Lecturer in Public Health, drafted the protocol, contributed to all sections of the report and drafted the final manuscript. K Dalziel, Research Fellow, conducted appraisals of relevant literature, contributed to the economic analysis and the analysis of the diffusion study and drafted the final manuscript. Dr A Walker, Health Economist, carried out the health economic analysis. Dr L McIntyre, Researcher, conducted the review of behavioural change and knowledge of HCV status. B Jenkins, Epidemiologist, drafted the sections on the epidemiology of HCV in the UK. Dr J Horne, Specialist Registrar in Public Health Medicine, helped to design and conducted the diffusion study. Dr P Royle, Information Scientist, carried out all searches and applied inclusion criteria, and commented on the draft report. Dr A Round, Senior Lecturer in Public Health, commented on the protocol and edited the final draft of the report.

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Appendix 1

List of search questions, search strategies and databases

Existing evaluations of screening for HCV

Search strategy

(hcv or hepatitis C) and (screen* or explode 'Mass-Screening'/MeSH)

Databases

- MEDLINE, 1996–May 2001
- EMBASE, 1996–July 2001
- PubMed, February 2001–January 2002
- DARE, August 2001, Internet <http://agatha.york.ac.uk/welcome.htm>
- NHS EED, August 2001, Internet <http://agatha.york.ac.uk/welcome.htm>
- HTA database, August 2001, Internet <http://agatha.york.ac.uk/welcome.htm>

Epidemiology of HCV infection amongst IDUs

Search strategy

(mortality or survival or life expectancy or epidemiology or 'Prognosis'/MeSH) and (explode 'Substance-Abuse-Intravenous'/MeSH or (intravenous near drug use*) or (intravenous near drug abuse*) or ivdu) and (hcv or hepatitis C)

Databases

- MEDLINE, 1990–May 2001
- EMBASE, 1989–July 2001

The prevalence of HCV infection amongst attenders at GUM clinics in England

Search strategy

((genitourinary near2 clinic*) or (genito-urinary near2 clinic*) or (gum near clinic*)) and (hcv or hepatitis C)

Databases

- MEDLINE, 1990–May 2001
- EMBASE, 1989–July 2001

The risk of acquiring HCV infection through sexual practices

Search strategy

Sex* and (transm* or risk*) and (hepatitis c or hcv)

Databases

- MEDLINE, 1990–May 2001
- EMBASE, 1989–July 2001

Epidemiology of HCV infection in the UK

Search strategy

epidemiology and (hcv or hepatitis c) and 'Great-Britain'/MeSH

Databases

- MEDLINE, 1990–May 2001
- EMBASE 1989–July 2001

Epidemiology of HCV serotypes in the UK

Search strategy

(seroepidemiolog* or epidemiolog*) and (serotype* or genotype*) and (hepatitis c or hcv) and (england or wales or britain or uk)

Databases

- MEDLINE, 1990–May 2001
- EMBASE, 1989–July 2001

Utility of HCV disease states

Search strategy

(hepatitis c or hep*c or hcv) and (utility or utilities or quality adjusted life year* or qaly)

Databases

- MEDLINE, 1966–January 2002
- EMBASE, 1988–January 2002

Sensitivity and specificity of diagnostic tests for HCV

Search strategy

(hcv or hepatitis c) and (sensitivity* or specificit* or false negative* or accuracy or predictive value* or likelihood ratio* or 'Diagnostic-Use'/MeSH or 'Diagnosis'/MeSH)

Databases

- MEDLINE, 1990–May 2001
- EMBASE, 1989–July 2001

Liver biopsy and HCV

Search strategy

(biopsy or biopsies) and (harm* or adverse) and liver and (hepatitis c or hcv)

Databases

- MEDLINE, 1990–May 2001
- EMBASE, 1989–July 2001

Does knowledge of HCV or HIV status change risk-taking behaviour?

Search strategies

- (hepatitis or hcv or hiv or aids) and status and (behavior or behaviour) and knowledge
- (hepatitis or hcv or hiv or aids) and (risk or know*) and (behavior or behaviour)
- hepatitis and risk and (behavior or behaviour) and (know* or status)
- (risk* near behavi*) and drug and (positive or serostatus or seropositive) and reduc*
- (hcv or hepatitis) and (positive or serostatus or seropositiv*) and risk* and behavi*

Databases

- MEDLINE, 1990–May 2001
- EMBASE, 1989–July 2001
- PubMed, February 2001–August 2002
- Science Citation Index, 1981–August 2001
- Social Sciences Citation Index, 1981–August 2001
- PsychINFO, 1984–August 2001
- HealthPromis

The Cited Reference Searching function in Science Citation Index and Social Sciences Citation Index was also used to locate articles that had cited any relevant references identified in the searches above.

Pegylated interferon for HCV

Search strategy

(pegylated or pegasys or peg-ifn or peginterferon or peg-interferon or polyethylene glycol or peg-intron or rebetron) and (hepatitis c or hcv)

Databases

- MEDLINE, 1966–May 2001
- EMBASE, 1981–June 2001
- PubMed, June 2001–December 2001
- Science Citation Index, 1981–August 2001 (limited to meeting abstracts only)
- Web of Science Proceedings, 1990–August 2001
- BIOSIS, 1985–August 2001 (limited to meeting abstracts only)

Combination therapy (ribavirin plus interferon-α) for HCV

Search strategies

- (explode 'Interferon-Alpha'/MeSH or interferon*) and (ribavirin* and 'Ribavirin'/MeSH) and (random* or (systematic near review*) or (systematic near overview*) or (meta-analys* or metaanalys*))
- (explode 'Interferon-Alpha'/MeSH or interferon*) and (ribavirin* and 'Ribavirin'/MeSH) and ((PT=RANDOMIZED-CONTROLLED-TRIAL) or (PT=META-ANALYSIS))

Databases

- MEDLINE, 1999–October 2001
- EMBASE, July 1999–November 2001
- PubMed, June 2001–December 2001
- Cochrane Controlled Trials Register, 2001, issue 4
- Science Citation Index, 1999–August 2001 (limited to meeting abstracts only)
- Web of Science Proceedings, 1990–August 2001
- BIOSIS, 1999–August 2001 (limited to meeting abstracts only)

Additional searches

Documents were downloaded from the following websites:

- Australian Department of Health and ageing, HIV/AIDS and hepatitis C <http://www.health.gov.au/pubhlth/publicat/hac.htm>
- USA Center for Disease Control, National Center for Infectious Diseases, viral hepatitis C <http://www.cdc.gov/ncidod/diseases/hepatitis/c/>

- Department of Health – prevalence of HIV and hepatitis infections in the United Kingdom, 1999 <http://www.doh.gov.uk/hivhepatitis99.htm>
- European Medicines Evaluation Agency – PegIntron <http://www.eudra.org/humandocs/humans/epar/pegintron/pegintron.htm>
- NHS Scotland – Scottish hepatitis C surveillance data <http://www.show.scot.nhs.uk/scieh/infectious/hepatitisc/infhepatitisc.html>
- National Institutes of Health Management of Hepatitis C Consensus Development Conference Statement, March 24–26, 1997 <http://odp.od.nih.gov/consensus/cons/105/105_statement.htm>
- Public Health Laboratory Service <http://www.phls.co.uk/facts/Hepatitis/Hep%20C/hepc.htm>
- WHO <http://www.who.int/inf-fs/en/fact164.html>

Appendix 2

National Survey of Screening for Hepatitis C

NHS HEALTH TECHNOLOGY ASSESSMENT PROGRAMME

NHS NATIONAL SCREENING COMMITTEE

This questionnaire survey is being carried out by the University of Exeter on behalf of the Department of Health's National Screening Committee and as part of a wider study of screening being carried out for the NHS Health Technology Assessment Programme. The survey is looking at screening, that is, offering testing to those who do not have symptoms and have not approached the service and requested a test. If you have any enquiries regarding the survey, please telephone Dr Ken Stein on 01392 207385 or Fax 01392 207377.

Thank you for your help.

Your name _____

Job title _____

Organisation _____

Address _____

_____

_____

Email _____

Telephone _____

Fax _____

1. (a) Is your organisation/department involved in screening/testing for hepatitis C?

Yes ☐ No ☐

If yes, answer 1(b) then go to section A
If no, go to section B

(b) Does your organisation offer hepatitis C testing on demand?

Yes ☐ No ☐

A. Please complete this section if your organisation is involved in screening for hepatitis C

2. This question asks about how screening/testing started in your organisation

(a) When did screening/testing start?

_____

(b) Who is eligible for screening/testing? Please give specific detail where possible

_____
_____
_____

(c) Is screening/testing offered once only or repeated?

Once only ☐ Repeated ☐

(d) If screening/testing is repeated, is there a policy about the interval between screening being offered?

Yes ☐ No ☐

If yes, what is the interval: _____ months

Why was this interval chosen?

_____
_____

(e) What organisations were involved in taking the decision to start screening/testing?

Only your organisation Yes ☐
Your local health authority Yes ☐
Other organisations (please specify) Yes ☐

_____
_____

(f) Please indicate your opinion on how influential the following were to the decision to start screening/testing:

	Very influential	Moderately influential	Slightly influential	Not influential
Public and patient views	☐	☐	☐	☐
Professional views	☐	☐	☐	☐
National policy	☐	☐	☐	☐
Regional policy	☐	☐	☐	☐
Evidence for effectiveness	☐	☐	☐	☐
Value for money (cost-effectiveness)	☐	☐	☐	☐

(g) What source(s) of evidence for the effectiveness or cost-effectiveness of screening/testing informed the decision?

_____
_____
_____

3. This question asks about the process of screening/testing for hepatitis C in your organisation

(a) What serological test(s) is/are used to screen for hepatitis C?

_____

_____

(b) What virological test(s) is/are used as confirmation following positive serology

_____

_____

(c) What information is given to people at the time of screening/testing?
(*some people call this pre-test counselling*)

_____

_____

(d) Which health professional carries out screening/testing?

Nurse	Yes ☐	No ☐
Doctor	Yes ☐	No ☐
Other health professional (please specify)	Yes ☐	No ☐

_____

Further details:

_____

_____

(e) Approximately how long do you think it takes to offer hepatitis C screening/testing to each person using your service, including the provision of necessary information prior to screening/testing?

_____

(f) How are people informed of their test result?

If hepatitis C negative:	please tick
In writing	☐
Via their GP	☐
When they return to the service	☐
Other (please specify)	☐

_____

If hepatitis C positive	please tick
In writing	☐
Via their GP	☐
When they return to the service	☐
Other (please specify)	☐

_____

(g) For people who test positive, is counselling offered at the time the test result is given?

Yes ☐ No ☐

(h) Who provides counselling to people who test positive, and approximately how long is spent with each person?

	please tick	*Approximate time spent*
Nurse (please give grade)	☐	_____
Doctor (please give grade)	☐	_____
Other health professional	☐	_____
(please specify) _____		
Referred to another organisation	☐	_____
(please specify) _____		

(i) What treatments are available for people with hepatitis C in your area?

	Yes	No	Don't know
Interferon monotherapy	☐	☐	☐
Interferon + ribavirin combination therapy	☐	☐	☐
Pegylated interferon monotherapy or combination therapy	☐	☐	☐

(j) Are there eligibility criteria for treatment? Yes ☐ No ☐ Don't know ☐

If yes, please state the criteria:

_____
_____
_____
_____
_____
_____

(k) Who is responsible for initiating treatment?
Please specify the organisation and, if possible, the individuals involved

(l) Who is responsible for continuing treatment once initiated?
(This may be the same as above)

Name(s)	Job title(s)	Organisation

_____
_____
_____
_____

(m) Has any evaluation or audit of the screening/testing programme for hepatitis C been carried out?

Yes ☐ No ☐

If yes, please give a contact name and address/telephone/email for further information

_____
_____
_____

(n) If possible, please give the following information:

Number of people who used the service: _____
Number of people who were tested for hepatitis C: _____
Number of people who tested positive: _____
Number of people who accepted treatment: _____
Number of people who showed a response: _____

Please specify the period covered by the information you can give.
For the period: _____to _____

Please give the source for the information you have given:

	please tick
Personal estimate	☐
Survey/audit of service	☐
Routinely collected service information	☐
Other (please specify)	☐ _____

4. Do you have any further comments on screening/testing for hepatitis C?

_____
_____
_____
_____
_____
_____
_____
_____

B. Please complete this section if your organisation is not involved in screening/testing for hepatitis C

(a) Has screening/testing for hepatitis C been considered within the organisation?
Yes ☐ No ☐

(b) If no, are there plans to carry out screening/testing for hepatitis C?
Yes ☐ No ☐

If no, thank you very much — you have completed the questionnaire

(c) If yes, when was the decision taken not to screen/test for hepatitis C?

_____

(d) Please describe who was involved in the decision regarding hepatitis C screening/testing

_____
_____
_____

(e) Please indicate your opinion on how influential the following were to the local decision NOT to start screening/testing

	Very influential	Moderately influential	Slightly influential	Not influential
Public and patient views	☐	☐	☐	☐
Professional views	☐	☐	☐	☐
National policy	☐	☐	☐	☐
Regional policy	☐	☐	☐	☐
Evidence for effectiveness	☐	☐	☐	☐
Value for money (cost-effectiveness)	☐	☐	☐	☐

(f) Any further comments you may have on screening/testing for hepatitis C

_____
_____
_____
_____
_____

Thank you very much indeed for completing the questionnaire

Please return this questionnaire in the pre-paid envelope provided

Appendix 3

Data extraction tables

Economic evaluations of screening programmes for HCV

Included studies

Study	Design	Comments on methods	Results/conclusions	Relevance
Leal and Stein, 1998[84] (Leal *et al.*, 1998[77] refines and details the study of IDUs from this study)	CUA of the first year of screening and treatment for HCV in IDUs and GUM clinics The model was based on the assumption of 5600 IDUs in the south and west regions of England and 56,000 people/year attending GUM clinics A combination of ELISA, RIBA and PCR were used to screen for HCV. Treatment was with interferon The economic evaluation was performed using a simple spreadsheet model and incorporated the following parameters: number of people presenting, eligibility for screening, acceptance of screening, yield of screening tests, acceptance and risks of liver biopsy, adherence to treatment and incidence of adverse effects The benefits as a result of screening and treatment were measured in QALYs and were calculated on the basis of disbenefits avoided The costs and averted costs were from the NHS perspective and were associated with screening, diagnosis, treatment and prevention of HCV consequences. These estimates were combined into a summary cost–utility estimate and subjected to sensitivity analyses	***Question*** Clear ***Description of competing alternatives*** There was clear information on the proposed screening population and setting. The diagnostic and treatment steps were outlined. No comparison was made with the likely events without screening ***Programme effectiveness*** Effectiveness of treatment was derived from a meta-analysis of monotherapy as were adverse events. Evidence for behaviour changes and acceptance rates were from observational studies. Evidence for the screening tests came from three diagnostic studies ***Perspective*** NHS (south and west regions) ***Costs and consequences*** It was unclear whether the costs of screening tests included capital costs. Costs of counselling, testing, biopsy, treatment, adverse events and monitoring were included. Utilities were also included. Many of the sources of costs were arbitrary and lacked an evidence base, based on estimates from single hospitals. Utilities were derived from a single physician's estimates. Little consideration was taken of the costs incurred by patients withdrawing from the screening programme or what may have happened to them. The study did not include estimates for early/effective treatment in the absence of screening ***Measures of outcomes*** Outcomes were measured as QALYs ***Discounting*** Benefits were discounted at 3% and costs were discounted according to the assumption that they may not be incurred for 20 or 30 years ***Incremental analysis*** The analysis was incremental over a 'no screening' comparison ***Handling uncertainty*** Detailed sensitivity analyses were presented for most parameters ***Other issues of concern*** The model was very sensitive to some adherence figures for which there was only one available study. This simplistic model did not accurately represent the natural history of HCV. A Markov model would be required	The costs of the prevalence rounds of screening in IDUs and GUM clinic attenders were estimated at about £700,000 and £1,000,000, respectively, in the south and west regions Given the study assumptions, screening IDUs was likely to identify 1426 people with HCV, of whom 270 would be eligible for treatment and 20 would respond to interferon-α. This gave a cost of £10,177/QALY Given the study assumptions, screening GUM clinic attenders was likely to identify 1029 people with HCV, of whom 195 would be eligible for treatment and 14 would gain long-term benefits. This gave a cost of £27,125/QALY Sensitivity analyses showed a range of possible cost/QALYs: £12,580–194,026 for GUM clinic attenders and £3333–81,438 for IDUs Many important uncertainties surrounded the assumptions used to estimate the long-term effectiveness of screening and treatment. Further research is required	The main limitations were the lack of accurate data to inform the model and the inability of the model to reflect the natural history of HCV. There was little attention paid to people withdrawing from the screening programme Some components were outdated and new studies and treatments are now available Relevant to the UK setting, IDUs and GUM clinics

continued

Economic evaluations of screening programmes for HCV *contd*

Included studies *contd*

Study	Design	Comments on methods	Results/conclusions	Relevance
Ishizuka, 1999[85]	Cost–benefit analysis of screening in the Saga Prefecture, Japan, 1993–1996 HCV screening was conducted as part of general medical screening between 1993 and 1996 ("health project for the aged"). Analysis was based on the results for 1995 The screening test used was second-generation ELISA with a positive result defined as a titre of $\geq 2^5$ and carriers defined as people with an antibody titre of $> 2^{11}$. Of carriers, 78% were assumed to have symptomatic CAH and 35% of the rest (asymptomatic) were assumed also to be recipients of treatment Further investigation was by biopsy, involving a 4-day inpatient stay. Treatment was with interferon monotherapy, including a 2-week inpatient stay, and assuming a complete responder rate of 29.8% at 1 year Adjustment for the detection of HCV in the absence of a screening programme was made by considering the number of people who would be detected by existing screening of liver function using aspartate transaminase and by comparison between districts with and without the screening programme during 1993 Costs of screening included establishment of the screening programme and for further investigation and treatment. Costs included loss of earnings to attend for further investigation and treatment Benefits were defined as savings to the medical system and losses of earnings prevented through avoidance of HCV consequences A natural history model was developed using mean times to progression between HCV health states, stratified by age and based on the age and sex distribution of people identified during screening	***Question*** Clear ***Description of competing alternatives*** Details on the process of screening and population coverage were limited, i.e. setting and other activities performed as part of the health project for the aged and characteristics of the population served ***Programme effectiveness*** Mixed basis for analysis. Local information on number of cases found, but not on number of people screened and adherence to subsequent investigation and treatment ***Perspective*** Two perspectives were presented: the Japanese health service and participants in the screening programme (represented by loss of earnings) ***Costs and consequences*** Costs appeared to be identified and valued appropriately for the perspectives concerned. However, the monetary value of benefits was calculated only as savings to the health service and prevented loss of earnings and was, therefore, limited. No valuations of the health states averted by successful treatment were presented ***Measures of outcomes*** Outcomes were measured in financial units, but this aspect of the analysis was limited ***Discounting*** 3% on costs and benefits (1 and 5% used in sensitivity analyses) ***Incremental analysis*** Unclear how the calculation of cost:benefit allowed for identification of HCV-positive people outside the screening programme, although methods presented two approaches ***Handling uncertainty*** Limited sensitivity and threshold analyses ***Other issues of concern*** Model of future health states was very simplistic. The applicability to the UK population and health service was limited	Prevalence of HCV was relatively high at 8.3% Benefit:cost ratios were calculated: 1.71 using only direct costs and benefits and 2.31 using total costs and benefits Results were sensitive to the discount rate and the response rate to interferon therapy. The authors concluded that the programme was cost-saving when the antibody-positive rate was > 1%, even if the response rate was as low as 20%	There were significant methodological weaknesses External validity was low for the UK: costs were not applicable to the UK; there was a high general population prevalence; there were no details of the nature of the population; the screening test is now outdated and patterns of care were not typical of the UK (e.g. 2-week inpatient stay for treatment)

continued

Economic evaluations of screening programmes for HCV *contd*

Included studies *contd*

Study	Design	Comments on methods	Results/conclusions	Relevance
Desenclos *et al.*, 1997[90]	Analysis of screening strategies for HCV Comparison of ALT and risk-factor approaches to screening 6238 social insurance beneficiaries were screened using third-generation ELISA yielding 73 cases. A case–control study was then used to investigate risk factors associated with HCV. Screening strategies based on risk factors were then compared to screening based on ALT levels (using a cut-off level derived from the overall population based on two French population-derived values used to exclude blood donors: (a) N (exclusion value) = mean + 2SD or (b) $N = 10^{mean + 1.96SD}$ Sensitivity, specificity and PPV of different approaches to screening were compared. Receiver–operator characteristic curves (relationship between false-positive and false-negative rates) were calculated	***Question*** Well defined, although the focus was on the effectiveness of screening strategies in identifying cases more than on economic considerations ***Description of competing alternatives*** Clear ***Programme effectiveness*** This was the main focus of the study – to compare two approaches to identifying people at high risk of HCV. Cases and controls were drawn from the same population, minimising selection bias. Methods for multivariate analysis were not stated. There was no matching of cases and controls The interviewer identifying possible risk factors was blind to case or control status of subjects, but blinding was not tested. There were no sources of the risk-factor information other than the questionnaire used ***Perspective*** French healthcare system ***Costs and consequences*** Costs of diagnostic tests were used as the basis for the cost/case detected. No other costs were included (e.g. counselling, further diagnostic tests and treatment). Cost base year was not specified ***Measures of outcomes*** Reasonable ***Discounting*** Not relevant, as costs and consequences occurred at the same and current time ***Incremental analysis*** No ***Handling uncertainty*** None ***Other issues of concern*** Limited external validity for the UK	Different thresholds were based on ALT N investigated. 1.2N based on approach (a) gave a "good compromise between cost and efficiency": a sensitivity of 50%, a specificity of 95.5%, a PPV of 11.5% and a cost/case of FF1600 11 of 23 risk factors had a specificity of > 90% leading to 1–8.7% of the population being tested. The highest sensitivity was a blood transfusion before 1991 (33%) for a PPV of about 5%. Being an IDU had a sensitivity of 29.2% and a PPV of 32.3%. Five or more pregnancies showed a sensitivity of 24.4% and a PPV of 11.5% Six risk factors with best specificity gave a sensitivity of 52.8% and selected 9.5% of the population for testing, leading to a PPV of 6.3% and a specificity of 91%. The cost/case was FF2900 Being an IDU or having a blood transfusion before 1991 selected 8.8% of the population for testing with a sensitivity of 58.3%, a specificity of 91.8%, a PPV of 7.6% and a cost/case of FF2400	Generalisability was uncertain – social insurance beneficiaries in France have no analogue in the UK Cost estimations were very limited and analysis was not incremental ALT is not generally available in the context of screening of IDUs or GUM clinic attenders, and is more relevant to screening in addition to routine blood testing, e.g. in the context of a medical screening examination, which is unusual in these populations in the UK

continued

Economic evaluations of screening programmes for HCV *contd*

Included studies *contd*

Study	Design	Comments on methods	Results/conclusions	Relevance
Rotily *et al.*, 1997[86]	CEA of screening test combinations in the following populations (prevalence): the general population (0.9%), transfusion recipients (7%), haemophiliacs (66%), IDUs (80%) and haemodialysis recipients (20%) The following test combinations were examined (except where noted, tests are in sequence): • PCR • PCR + PCR • ELISA • ELISA + PCR • ELISA and ELISA in parallel • ELISA + ELISA • ELISA + RIBA • ELISA + RIBA + PCR • ALT • ALT + ELISA • ALT + PCR	***Question*** Well defined ***Description of competing alternatives*** Limited – only true-positives were counted. No allowance was given for additional health service contact for false-positives ***Programme effectiveness*** Third-generation ELISA effectiveness data was drawn from a single study in a low-risk population. Quality and precision of effectiveness data was not described ***Perspective*** French healthcare system ***Costs and consequences*** Test costs were included in FF, but no year was stated. The cost of consultation with a generalist was included (FF100) but there were no other associated costs. The source of test cost data was not stated, and consultation costs were from reimbursement schedules ***Measures of outcomes*** The primary outcome of interest was true-positive cases identified. Other outcomes were number of false-positives and true- and false-negatives ***Discounting*** Not relevant, as costs and consequences occurred at the same time, although limited ***Incremental analysis*** Average cost-effectiveness ratios were quoted for each screening strategy, and thus effect of moving from one strategy to another was not demonstrated ***Handling uncertainty*** Uncertainty in effectiveness and prevalence estimates were not addressed. Sensitivity analyses were conducted by varying the weights attached to outcomes other than true-positives in the decision tree. Results were not reported in detail ***Other issues of concern*** Adherence to screening, diagnosis and treatment were not addressed. Organisational implications of screening were not addressed	In all the populations studied, ELISA alone had the lowest average cost-effectiveness ratio (FF per true-positive detected): General population = FF42,985 Transfusion recipients = FF7034 Haemophiliacs = FF774 IDUs = FF645 Haemodialysis recipients = FF2579 However, the number of false-positives was high for this strategy, which is not taken into account in the cost-effectiveness ratio. In the general population, over 3 million people would be false-positives PCR followed by PCR brought the lowest number of false-positives and false-negatives, but at high cost The favoured strategy suggested by the authors was ELISA followed by a confirmatory test (PCR or RIBA)	Limited relevance Costs were for the French healthcare system and economic analysis was limited in both scope and quality

continued

Economic evaluations of screening programmes for HCV *contd*

Included studies *contd*

<table>
<tr><th>Study</th><th>Design</th><th>Comments on methods</th><th>Results/conclusions</th><th>Relevance</th></tr>
<tr>
<td>Lapane et al., 1998[87]</td>
<td>Analysis of the performance and cost-effectiveness of approaches to screening based on the USA National Hepatitis Surveillance Program

13,997 people from 40 USA urban centres were self-selected for HCV testing (second-generation ELISA)

Risk-profile questionnaire was completed by 66% of respondents. It was used to inform a logistic regression analysis of determinants of HCV positivity, which were then explored in four predictive models:

(1) A receiver–operator characteristics curve was generated from the regression analysis using different cut-offs of risk. A 7% predicted probability of HCV was based on a history reported as the most favourable balance between sensitivity and specificity and this was used as the cut-off for serological testing. Model 1 was based on an individual risk prediction equation derived from significant regression coefficients in the questionnaire analysis

(2) Serological testing in individuals at significant risk was based on any positive response to questions that were grouped as socially intrusive (history of being an IDU or sexual intercourse with an IDU) and non-socially intrusive (age 30–49 years, transfusion history and male gender)

(3) Serological testing in those at significant risk was based on answers to two or more non-socially intrusive questions

(4) Serological testing was based on abnormal ALT levels

Cost/case detected was calculated</td>
<td>Programme effectiveness
Screening test was second-generation ELISA. Only those positive on ELISA were tested further (using RIBA). Screening test accuracy was, therefore, probably less than current technologies can achieve

Cut-off values for ALT employed in model 4 were not stated

Perspective
Unclear. USA healthcare system

Costs and consequences
Cost/case detected was based on USA cost data from nine academic institutions (costs were unlikely to be typical of non-academic institutions or relevant to the UK). The base year was not stated. Only costs of diagnostic tests were included – counselling time and consultation time were excluded. Costs and benefits of treatment were not incorporated

Measures of outcomes
Cost/case detected. Limited measure of outcome, as not all cases detected would be eligible for treatment and there was limited evidence that knowledge of HCV status had intrinsic value

Discounting
Not relevant, as costs and consequences were held to occur at the same time. No long-term consequences were considered

Incremental analysis
Yes

Handling uncertainty
None

Other issues of concern
Self-selected sample with high prevalence of HCV (7%), although intercept on regression line was similar to the USA overall prevalence estimate (1.5%)

The 66% response rate to the questionnaire was reasonable, but there was missing data in responses. This was handled in the analysis using dummy variables, but the quantity and domains of missing data were not discussed, and thus impact on the analysis was hard to predict

Validity of the questionnaire was not discussed</td>
<td>Performance characteristics of screening strategies:

<table>
<tr><th>Model</th><th>Prevalence</th><th>PPV</th><th>Sensitivity</th><th>NPV</th><th>Specificity</th></tr>
<tr><td>1</td><td>20%</td><td>22%</td><td>65%</td><td>97%</td><td>84%</td></tr>
<tr><td>2</td><td>29%</td><td>16%</td><td>69%</td><td>97%</td><td>74%</td></tr>
<tr><td>3</td><td>25%</td><td>14%</td><td>53%</td><td>96%</td><td>77%</td></tr>
<tr><td>4</td><td>12%</td><td>34%</td><td>63%</td><td>97%</td><td>92%</td></tr>
</table>

Incremental cost-effectiveness:

<table>
<tr><th>Model</th><th>Cases/ 100 screens</th><th>Cost/ 100 screens (US$)</th><th>Mean cost/case (US$)</th><th>Marginal cost/ case detected (US$)</th></tr>
<tr><td>1</td><td>4.4</td><td>1571</td><td>357</td><td>Dominates</td></tr>
<tr><td>2</td><td>4.6</td><td>2020</td><td>439</td><td>285</td></tr>
<tr><td>3</td><td>3.5</td><td>1706</td><td>487</td><td>Base case</td></tr>
<tr><td>4</td><td>4.1</td><td>4292</td><td>1047</td><td>4310</td></tr>
</table>
</td>
<td>Relevance to the UK was low

Economic evaluation was weak with limited scope from USA perspective

Technology was not relevant to the UK

There were selection bias problems with the survey</td>
</tr>
</table>

continued

Economic evaluations of screening programmes for HCV *contd*

Included studies *contd*

Study	Design	Comments on methods	Results/conclusions	Relevance
Kaur *et al.*, 1996[88]	Observational study based on the USA National Hepatitis Surveillance Program (see Lapane *et al.* for description of the survey) Major objective of the study was exploration of risk factors for HCV (and HBV) infection. However, cost/case detected and cost/durable response were calculated	***Question*** Well defined ***Programme effectiveness*** Second-generation ELISA with RIBA confirmation used for screening ***Perspective*** USA healthcare system ***Costs and consequences*** Only costs of diagnostic tests and two physician visits were included. Items omitted include: pre-test counselling, liver biopsy and treatment (cost of therapies and medical attendance costs). No base year for costs was given ***Measures of outcomes*** Estimates of durable response to monotherapy were used (single trials): 10 and 25% ***Discounting*** Not considered ***Incremental analysis*** No ***Handling uncertainty*** None ***Other issues of concern*** Consideration of adherence to investigation and treatment was limited. It was assumed that 5% of those screened positive would be lost to follow-up and that 10–20% would be excluded from treatment	Cost/case detected was estimated as US$917–1246 Cost/durable response was estimated as US$6223–15,764	Not a comprehensive evaluation of a screening programme Economic analysis was weak and not relevant to the UK in 2002

continued

Economic evaluations of screening programmes for HCV *contd*

Excluded studies

Study	Design	Comments on methods	Results/conclusions	Relevance
Fischer *et al.*, 2000[89]	The project had two objectives: • to develop and evaluate a risk assessment tool derived from routine data available on enrolees of a USA Health Maintenance Organisation • to carry out screening of healthcare workers in the Health Maintenance Organisation The risk assessment tool was developed in a case–control study. Cases (n = 4400) were people with presumed HCV diagnosis (codes were HCV, hepatitis unspecified and liver disorders with HCV as a possible cause) and controls were a random sample from enrolees (n = 4400). Data from the previous 5 years on cases and controls were analysed for possible risk factors using contingency analysis and classification tree analysis. Hepatitis A or HBV, liver disorders and alcohol problems emerged as the most important predictors. Other predictors were included based on existing literature (there were no details of methods for identifying or including possible candidates) – coagulation disorders, cocaine use, dialysis, other drug problems, HIV and blood transfusion before 1992 Two groups were invited for screening: people identified as at risk using the risk factors noted (n = 5764) and a control group (n = 7139) who had codes for "miscellaneous symptoms", but not risk factors as above, chosen as preferable to a random sample because a random sample would include healthy enrolees who do not use the Health Maintenance Organisation People were invited by letter to participate in screening, which was based on a single PCR test Screening invitees completed a risk-factor questionnaire to enable evaluation of the risk assessment tool as a means of identifying people at risk of HCV Uptake of screening was calculated as a simple proportion of those invited	Definition of cases in the risk assessment development stage was not rigorous, calling into question the validity of the assessment. For example, a history of alcohol problems may have predicted different types of hepatitis differently, but this would not be apparent in the analysis because cases included "hepatitis unspecified" Exposures may have been earlier definitions of "case-ness", e.g. history of liver disorders would be expected to predict a case of liver disorder No details of the strengths of the associations between exposures and cases were given for the risk assessment stage. Confounding was a potentially significant problem – HBV may have been a confounder for injecting drug use, although the purpose of the analysis was to test whether routinely available data could be used to focus screening on high-risk groups The actual Health Maintenance Organisation population considered for screening was not given, therefore, it was not possible to calculate what % of the population was invited on the basis of the risk assessment tool Rationale for the selection of the control group in the screening sample was difficult to understand. The reference population from the study was, therefore, not the entire enrolled population but a subset of service users. It is difficult to generalise from this People with a known diagnosis of HCV were excluded from the screening stage of the project. However, the risk assessment stage acknowledged that the coding of HCV was poor within the Health Maintenance Organisation. Whether cases identified through screening were truly unknown was not reported The thresholds for factors in the questionnaire were not defined, e.g. unprotected sexual intercourse, frequent (*sic*) sexual partners The analyses were restricted to the performance of the risk assessment tool and participant questionnaire in identifying cases. In regression analyses, drug and alcohol use were combined	Of 12,903 people invited for screening, 1380 (10.7%) participated. Of those with a history of drug use, only 5% participated in screening 11 cases (0.8%) were identified through screening. Nine of the 11 cases identified were predicted as at risk from the routine data derived risk assessment tool The risk assessment tool identified one case for 50 screened, while the yield in the control group was one case per 170 screened	Not relevant Health Maintenance Organisation administrative data have no close equivalent in the UK Not a comprehensive evaluation of a screening programme The study had methodological weaknesses The population characteristics were different to those in the UK, and the screening test was not equivalent to an algorithm used in the UK

continued

Economic evaluations of screening programmes for HCV *contd*

Excluded studies *contd*

Study	Design	Comments on methods	Results/conclusions	Relevance
Perez, 1997[91]	Literature review of the efficacy and psychological impact of screening for HCV	Search strategy was limited to MEDLINE and EMBASE, 1989–1996 The study considered the advantages and disadvantages of screening, citing existing research where possible	No comprehensive evaluations were found The potential for screening to identify people with HCV and the effect on their risk of onward transmission of the virus was identified but not discussed in detail. Only one relevant study was identified No cost-effectiveness studies were identified Harms of liver biopsy were discussed, but only briefly, and there was no consideration of safety according to use of ultrasound control Acceptability of and adherence to screening and diagnosis was discussed, but no literature were identified No studies of the psychological effects of screening (on false- or true-positive cases) were identified	A literature review of the components of a screening programme, but no synthesis Now out of date. Not relevant as a comprehensive screening evaluation
Roque *et al.*, 1999[92]	Observational study describing screening in an anonymous HIV testing centre (Centre de Dépistage Anonyme et Gratuit) in Rouen, France ELISA + RIBA used for screening Screening was offered to 1045 people aged > 18 years from February to November 1997 Risk factors for a positive result on screening were identified	Not clear whether all attendees during the period were offered screening The univariate analysis was subject to confounding, e.g. tattooing and body piercing. The strongest association was with being an IDU – 69% of people were found to be positive versus 1.3% of those testing negative	98.4% accepted screening 16 people were positive (11 of them IDUs). Other significant risk factors were tattooing, history of being in prison and HIV infection (strong possibility of confounding)	Not relevant, as setting has no equivalent in the UK High acceptance rate not generalisable to other screening systems, as attendees were already seeking screening for HIV

Knowledge of HCV status and behavioural changes

Study	Country	Participants and design	Results	Comments
Cook *et al.*, 2001[94]	Northwest England (Wirral and Manchester)	407 drug users (341 IDUs and 45 non-injectors (21 were not included in the analysis because their HCV results were equivocal or there was insufficient blood taken)) were recruited through a range of techniques: contact with various drug services (first-time and ongoing service users); people self-referring to services for HIV, HBV or HCV testing and snowball sampling to identify people not in contact with services (n = 60) A cross-sectional questionnaire survey on behaviours ever, behaviours in the last 4 weeks and previous HCV tests	386 participants were included in the analysis. Of those tested, 53% were HCV positive, 19% had co-infection with HCV and HBV, 16% had differing current and self-reported previous HCV status and 18% of those reporting previous testing could not recall the result ***Drug-related behaviour*** **Tested versus untested** • Any sharing of injecting equipment: no significant difference (33.3 versus 41.3%) • Sharing of needles: no significant difference (5.1 versus 8.4%) • Sharing of syringes: no significant difference (5.1 versus 7.1%) • Sharing of spoons: no significant difference (28.3 versus 38.7%) • Sharing of filters: no significant difference (28.3 versus 29.8%) • Sharing of paraphernalia: no significant difference (32.3 versus 40.4%) **HCV positive versus HCV negative** • Any sharing of injecting equipment: no significant difference (41.7 versus 28.9%) • Sharing of needles: no significant difference (5.6 versus 6.7%) • Sharing of syringes: no significant difference (2.8 versus 8.9%) • Sharing of spoons: no significant difference (33.3 versus 29.8%) • Sharing of filters: no significant difference (36.1 versus 22.2%) • Sharing of paraphernalia: no significant difference (38.9 versus 29.8%)	Generalisability of the sample was difficult to assess. Some differences (non-significant) in prevalence were reported in the different groups suggesting that there may be important differences between the populations sampled Discrepancies and poor recollection among respondents suggested that there was a high probability of recall bias, although differences between recalled and tested HCV status may have been due to incident infections Social desirability bias was likely in responses, although may have been reduced by the presence of researchers during questionnaire completion. Unclear what steps were taken to minimise this source of bias The cross-sectional design of the study limited its potential to identify associations between knowledge of HCV status and behaviour, although no associations were found

continued

Knowledge of HCV status and behavioural changes *contd*

Study	Country	Participants and design	Results	Comments
Vidal-Trecan *et al.*, 2000[95]	Paris, France	612 consecutive patients were recruited from drug treatment services during 1994/1995. Those with severe mental disorders, AIDS and on methadone were excluded A face-to-face interview was conducted using questions from a national sexual health and lifestyle questionnaire and a bespoke drug behaviour questionnaire The following behaviours were assessed over the previous 6 months: • lending or borrowing paraphernalia • disinfection of equipment • multiple (> 1) sexual partners • repeat of previous HCV test in past 6 months ("consistent" HCV testing) Multivariate analyses adjusted for differences between groups due to age, sex, education, occupation, income, homelessness, marital status, sexual orientation and HIV serostatus	592 people were included in the analysis 63% reported "consistent" HCV testing versus 81% for HIV testing **Unknown status (never tested or no HCV testing in the past 6 months, *n* = 218) versus HCV negative (*n* = 171)** • Lending injecting equipment: no significant difference (OR = 0.9, 95% CI, 0.6 to 1.5) • Borrowing injecting equipment: no significant difference (OR = 0.9, 95% CI, 0.6 to 1.5) • Not using new equipment: HCV unknown significantly less likely not to use new equipment than HCV negative (OR = 0.4, 95% CI, 0.3 to 0.6) • Not using clean equipment: HCV unknown significantly more likely not to use clean equipment than HCV negative (OR = 1.9, 95% CI, 1.4 to 3.0) **HCV positive (*n* = 203) versus HCV negative (*n* = 171)** • Lending injecting equipment: no significant difference (OR = 1.4, 95% CI, 0.9 to 2.3) • Borrowing injecting equipment: no significant difference (OR = 1.2, 95% CI, 0.7 to 1.9) • Not using new equipment: HCV positive significantly less likely not to use new equipment than HCV negative (OR = 0.5, 95% CI, 0.3 to 0.8) • Not using clean equipment: no significant difference (OR = 1.4, 95% CI, 0.8 to 2.3)	Study population was stated as being similar to an IDU population in treatment in France. The generalisability to the UK is uncertain Recall and social desirability biases were possible, although the authors cited references to support the validity of their approach of using face-to-face interviews to reduce the latter People who were tested > 6 months previously would have been categorised as unknown, although their behaviour may have reflected a self-assessment of negative. The impact of this was uncertain, but may have masked different behaviours between never- and ever-tested individuals The cross-sectional nature of the study precludes any causal inference about the association between HCV status and behaviours

continued

Knowledge of HCV status and behavioural changes *contd*

<table>
<tr><th>Study</th><th>Country</th><th>Participants and design</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Ompad et al., 2000[97]</td>
<td>Maryland, USA</td>
<td>Longitudinal study in 106 recent IDUs recruited through community and street outreach

Participants were aged 15–30 years, had injected at least once in the previous 6 months and initiated drug use < 5 years previously

An interviewer-administered questionnaire was conducted covering:
• demographics
• drug use
• high-risk behaviours, including detail of sharing behaviours, such as indirect sharing (sharing of cookers, cottons, rinse water and backloading) and direct sharing (needle sharing)

HCV testing was performed using second-generation ELISA followed by RIBA confirmation

Counselling was given prior to HCV testing, and results were given 2 weeks later. Participants were then followed up at 6 and 12 months. Analysis was restricted to participants who had received their HCV result at least 3 months prior to follow-up (n = 106). Follow-up interviews were conducted face-to-face with investigators</td>
<td>HCV-negative (n = 50) and unknown groups (n = 10; i.e. those who were HCV positive but did not receive results) were combined for the analysis as “non-HCV” (n = 60)

Individuals in the HCV-positive group (n = 46) were less likely to be African–American and were slightly older at initiation of injecting (mean = 25 versus 23 years)

Results at follow-up are summarised in the table:

<table>
<tr><th rowspan="2">Sharing items</th><th colspan="2">None (%)</th><th colspan="2">No change (%)</th><th colspan="2">Increase (%)</th><th colspan="2">Decrease (%)</th></tr>
<tr><th>HCV positive</th><th>Non-HCV</th><th>HCV positive</th><th>Non-HCV</th><th>HCV positive</th><th>Non-HCV</th><th>HCV positive</th><th>Non-HCV</th></tr>
<tr><td>Cooker</td><td>17</td><td>27</td><td>28</td><td>17</td><td>24</td><td>28</td><td>30</td><td>28</td></tr>
<tr><td>Cotton</td><td>28</td><td>30</td><td>20</td><td>20</td><td>26</td><td>28</td><td>26</td><td>21</td></tr>
<tr><td>Rinse water</td><td>24</td><td>28</td><td>24</td><td>13</td><td>28</td><td>30</td><td>24</td><td>28</td></tr>
<tr><td>Backloading</td><td>7</td><td>5</td><td>54</td><td>63</td><td>22</td><td>18</td><td>17</td><td>13</td></tr>
<tr><td>Needles</td><td>54</td><td>47</td><td>17</td><td>5</td><td>17</td><td>27</td><td>11</td><td>22</td></tr>
</table>

Approximately 50% of those who acquired knowledge of HCV status showed no change or an increase in indirect sharing and approximately one-third showed no change or an increase in backloading or needle sharing

The comparisons between HCV positive and non-HCV groups were non-significant across all behaviours examined

The authors concluded that there was little evidence for behavioural changes following HCV testing, whether the results are positive or negative</td>
<td>Generalisability to the UK and to longer-term IDUs may be limited

The steps taken to reduce social desirability bias were unclear, although the second interview was face-to-face. However, social desirability bias might be expected to lead to a higher proportion reporting reduced sharing at follow-up

Recall bias remained a possibility – participants may have had better recollection of the 3 months to follow-up than of the 3 months prior to baseline testing

The measurement instrument was necessarily crude, and participants were asked to report whether they shared never, less than half the time, about half the time, more than half the time or always. Detailed results were not given. Respondents may have misclassified randomly in the central three categories producing changes between baseline and follow-up. There was some evidence for this in that similar proportions showed increased and decreased sharing for all indirect sharing behaviours across both groups. The underlying data were not given

It was a small sample, and, therefore, gives limited precision in the comparisons and raises the possibility of type II errors</td>
</tr>
</table>

continued

Knowledge of HCV status and behavioural changes *contd*

Study	Country	Participants and design	Results	Comments
Malliori et *al.*, 1998[96]	Greece	544 prisoners in two Greek prisons convicted of or awaiting trial for drug-related offences who reported a history of narcotic drug use A questionnaire was administered along with serological testing for HCV in 533 participants. Needle sharing during the past month was included, and compared between those reporting previous positive and negative HCV status on testing This was primarily an investigation of factors associated with HCV and HIV infection in prisoners	282/519 (54%) respondents reported having had a previous HBV or HCV test, and 9.4% were aware of a previous positive result The prevalence of anti-HCV positive was 58% overall and 80% among IDUs Almost all who reported drug use in prisons shared injecting equipment 39% of those who were aware of having had a previously positive HBV or HCV result reported sharing syringes in the previous month versus 37% of those who reported a negative previous test (not significant)	Denominators used in the analyses were inconsistent and without explanation HCV and HBV were not separated in the analysis of reported sharing by previous test result There was a low prevalence of reported HCV-positive status among the high proportion who reported having had a previous test and the high prevalence on the serological survey may have been due to poor recollection of actual HCV status The increase in sharing of injecting equipment in prisons may have been due to a lack of opportunity to use new or clean injecting equipment and, therefore, generalisability to outside prisons is limited

Diagnostic test performance of ELISA testing

Study	Design	Comments on methods	Results	Comments
Colin *et al.*, 2001[101]	***Participants*** A total of 4674 ELISA tests and 359 immunoblot tests were performed in ten studies. Four studies included blood donors, two included haemodialysed patients, one included patients with verified NANBH and one also included a panel of sera set up by a laboratory ***Diagnostic testing*** Three studies used ELISA 3.0 Ortho, one study used ELISA 3.0 Coras Core and one study used RIBA 3.0 (Ortho and Chiron) ***Gold standard reference tests used*** Four studies used HCV RNA as the gold standard with detection by PCR, one used ELISA 2.0 + RIBA 3.0, another used Ortho ELISA 3.0 and one study used PCR alone ***Outcomes*** Sensitivity and specificity	***Question focused?*** Yes. A third-generation test was compared to a HCV RNA detection test or serological test for diagnostic accuracy (according to sensitivities and specificities) ***Search strategy*** MEDLINE and EMBASE were searched and manual searching was conducted using the following terms: hepatitis C, serodiagnosis, sensitivity and specificity. This was a potentially narrow search strategy and some studies may have been missed. It was unclear what was meant by manual searching. The diagnostic filter was appropriate. There was a higher likelihood of publication bias with diagnostic studies ***Validity assessed?*** Yes, according to McMaster criteria: reference to a gold standard, appropriate spectrum of patients, description of setting and tactics for conducting the test and reproducibility and precision in performing and interpreting the test. Only studies with a diagnostic test and a reference test were included ***Results consistent?*** Heterogeneity was assessed in each group of patients using Fischer's exact test. The panels of sera assays using RIBA 3.0 as the reference test were not homogeneous and were, therefore, not pooled ***Appropriate analysis of results?*** Results were presented separately for high- and low-risk populations, each type of reference test, panels of sera and haemodialysed patients. Summary point estimates and CIs were only computed when the estimates of sensitivity and specificity were homogeneous. Subgroup analyses were performed when estimates were heterogeneous. CIs were computed using an exact method. Analysis of results was appropriate	Selected studies were grouped according to type of population at high and low risk and to the type of reference test used. Ten studies were included For the studies using HCV RNA detection as the gold standard, the sensitivity of ELISA 3.0 in patients with chronic liver disease was 97.2% (95% CI, 92 to 99). The sensitivity of ELISA 3.0 was 100% in haemodialysed patients, and 98.9% (95% CI, 94 to 100) on panels of sera The specificity of ELISA 3.0 was 100% in haemodialysed patients and patients with chronic liver disease RIBA 3.0 studies also used HCV RNA as the gold standard with a sensitivity and a specificity of 100% in patients with chronic liver disease. The sensitivity was 78.8% (95% CI, 65 to 89) and the specificity was 80% (95% CI, 30 to 96) in haemodialysed patients	The authors concluded that: "This analysis provides evidence for the good sensitivity and specificity of ELISA 3.0 assays, particularly in high-risk patient groups and confirms their use for screening in these populations. Further studies are needed to assess properly RIBA 3.0 in the general population and in risk patients." There was a clear research question and inclusion and exclusion criteria. The search for relevant studies was potentially narrow, especially considering the difficulty often arising in locating diagnostic studies and the potential for publication bias The analysis of the quality of included studies was appropriate, as was the pooling of homogeneous subgroups. However, pooling the results of few studies each with few patients does not always result in more information than the original studies. The results obtained by studying the panel of sera may not reflect a clinical population While the studies were split into more homogeneous groups of patients, we remain uncertain as to the homogeneity of setting and risk. We were also unable to determine the diagnostic threshold levels used to define positive and negative test results in the original studies and these may not have been homogeneous. We are uncertain of the generalisability of these results to IDUs and GUM clinic populations

Appendix 4

National Survey of Screening for Hepatitis C: results

TABLE 23 *Response rates for the survey of current practice*

	Number of questionnaires sent	Number of questionnaires returned (%)
HAs	95	69 (73)
Prisons	134	85 (63)
Drug services	140	86 (61)
GUM clinics	228	146 (64)
Total	597	386 (65)

TABLE 24 *Results of the question "Is screening carried out by your organisation?"*

Is screening carried out by your organisation?	HAs (*n*/*N* (%))	Prisons (*n*/*N* (%))	Drug services (*n*/*N* (%))	GUM clinics (*n*/*N* (%))
Yes	19/69 (28)	66/85 (78)	18/70 (26)	123/134 (92)
No	42/69 (61)	15/85 (18)	46/70 (66)	11/134 (9)
Not known	8/69 (12)	4/85 (5)	6/70 (9)	0/134 (0)

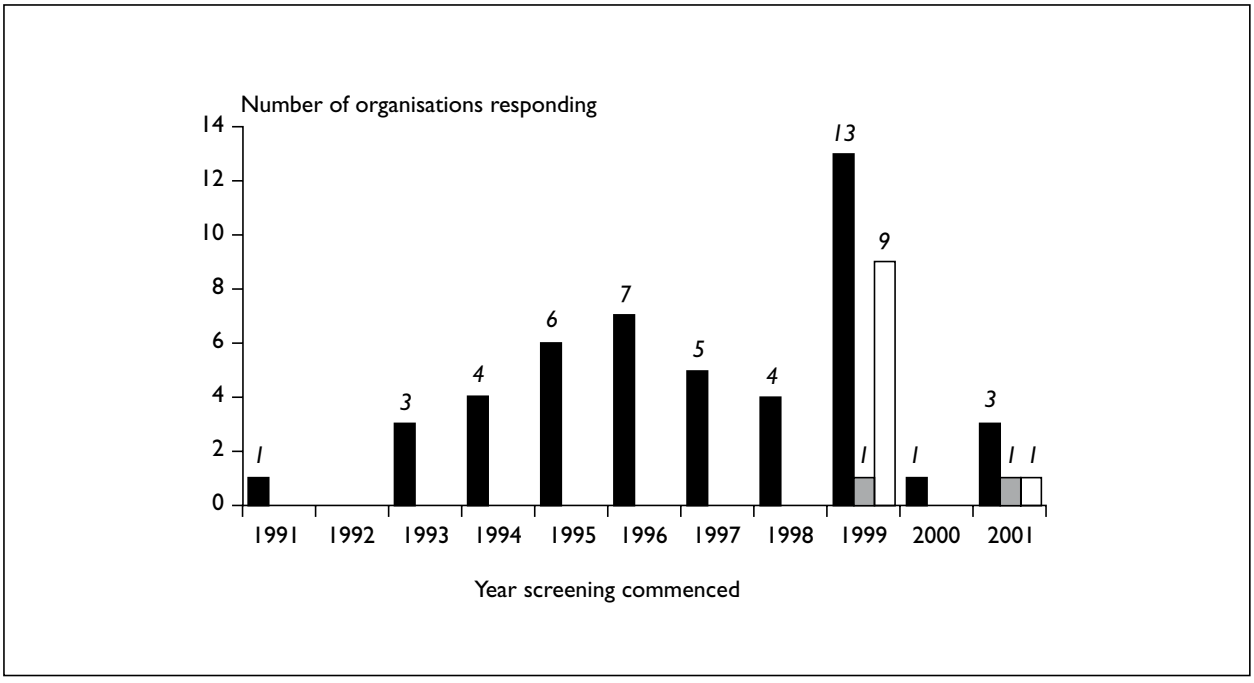

FIGURE 12 *Year that screening for HCV started in responding organisations (■, Prisons; ▨, drug services; □, GUM clinics)*

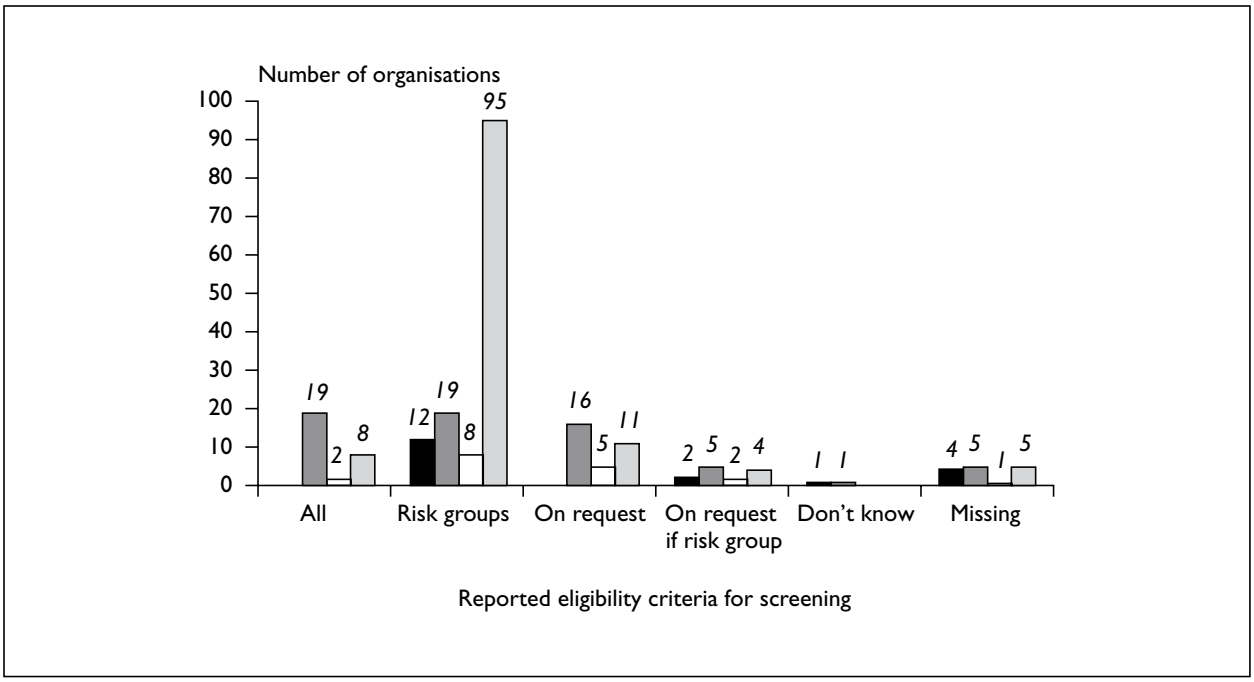

FIGURE 13 *Universal versus selected screening (■, HAs; ■, prisons; □, drug services; □, GUM clinics)*

TABLE 25 *Eligibility for screening*

Details of those eligible for screening	**HAs (*n*/*N* (%))**	**Prisons (*n*/*N* (%))**	**Drug services (*n*/*N* (%))**	**GUM clinics (*n*/*N* (%))**
Related to drug use	15 (71)	22 (67)	8 (57)	94 (33)
Related to sexual behaviour	0 (0)	5 (15)	1 (7)	60 (21)
Risk due to occupation	0 (0)	0 (0)	1 (7)	36 (12)
Risk due to medical procedure	1 (5)	0 (0)	0 (0)	19 (7)
Concurrent infections	1 (5)	0 (0)	0 (0)	28 (10)
Abnormal liver function tests	1 (5)	0 (0)	0 (0)	4 (1)
Pregnancy	1 (5)	0 (0)	0 (0)	0 (0)
Prisoners	2 (10)	1 (3)	0 (0)	0 (0)
Particular nationalities	0 (0)	1 (3)	0 (0)	5 (2)
"At-risk contact" not otherwise defined	0 (0)	4 (12)	4 (29)	43 (15)
Total responses	21	33	14	289

TABLE 26 *Organisations who screen once or screen repeatedly*

Does screening occur once only or is it repeated?	**HAs (*n* (%))**	**Prisons (*n* (%))**	**Drug services (*n* (%))**	**GUM clinics (*n* (%))**
Once only	5 (26)	18 (27)	3 (17)	19 (15)
Repeated	7 (37)	44 (67)	14 (78)	93 (76)
Missing	7 (37)	4 (6)	1 (5)	11 (9)
Total responses	19	66	18	123

TABLE 27 *Defined screening interval in organisations offering repeat screening*

If screening is repeated, is there a set interval?	HAs (*n* (%))	Prisons (*n* (%))	Drug services (*n* (%))	GUM clinics (*n* (%))
Yes	2 (29)	27 (61)	4 (29)	57 (61)
No	5 (71)	17 (39)	10 (71)	36 (39)
Total number that offer repeat screening	7	44	14	93

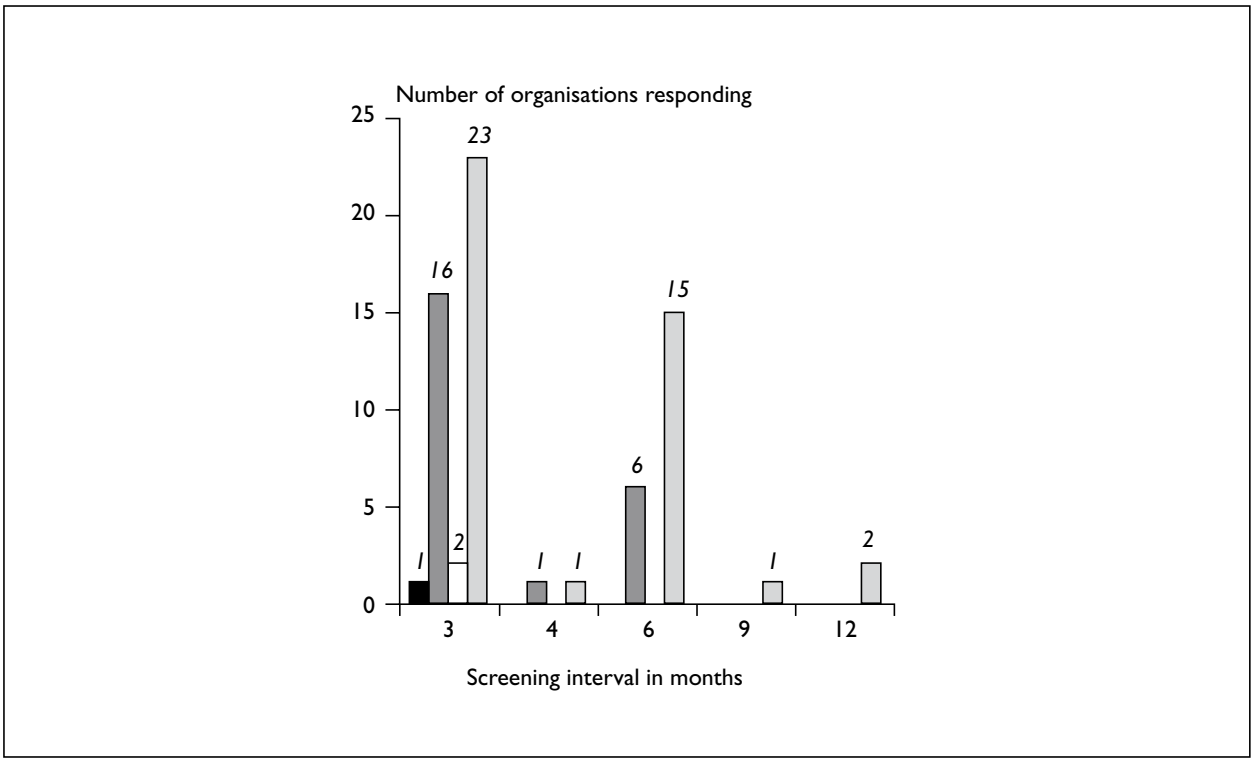

FIGURE 14 *Screening interval in organisations offering repeat screening (■, HAs; ■, prisons; □, drug services; □, GUM clinics)*

TABLE 28 *Justification of screening interval where repeat screening is offered*

Reasons given for interval	HAs (*n* (%))	Prisons (*n* (%))	Drug services (*n* (%))	GUM clinics (*n* (%))
Window period	0 (0)	15 (56)	0 (0)	32 (55)
Related to risk behaviour	0 (0)	1 (4)	0 (0)	12 (21)
Based on advice/guidelines	0 (0)	4 (15)	0 (0)	5 (9)
Linked to other tests	1 (100)	2 (7)	1 (100)	6 (10)
Manage demand	0 (0)	2 (7)	0 (0)	1 (2)
Confirm positive test	0 (0)	2 (7)	0 (0)	0 (0)
Convenience	0 (0)	1 (4)	0 (0)	1 (2)
Medicolegal re needlestick	0 (0)	0 (0)	0 (0)	1 (2)
Total responses	1	27	1	58

TABLE 29 *Organisations involved in the decision to start screening – responses from the HAs*

Organisation involved	Number of responses (*n* (%))
Prisons	3 (9)
HA	8 (23)
Medical	5 (14)
Microbiologist	1 (3)
Missing	4 (11)
Drug services	6 (17)
GUM clinics	1 (3)
Public health	2 (6)
Trust	4 (11)
None	1 (3)
Total responses	35

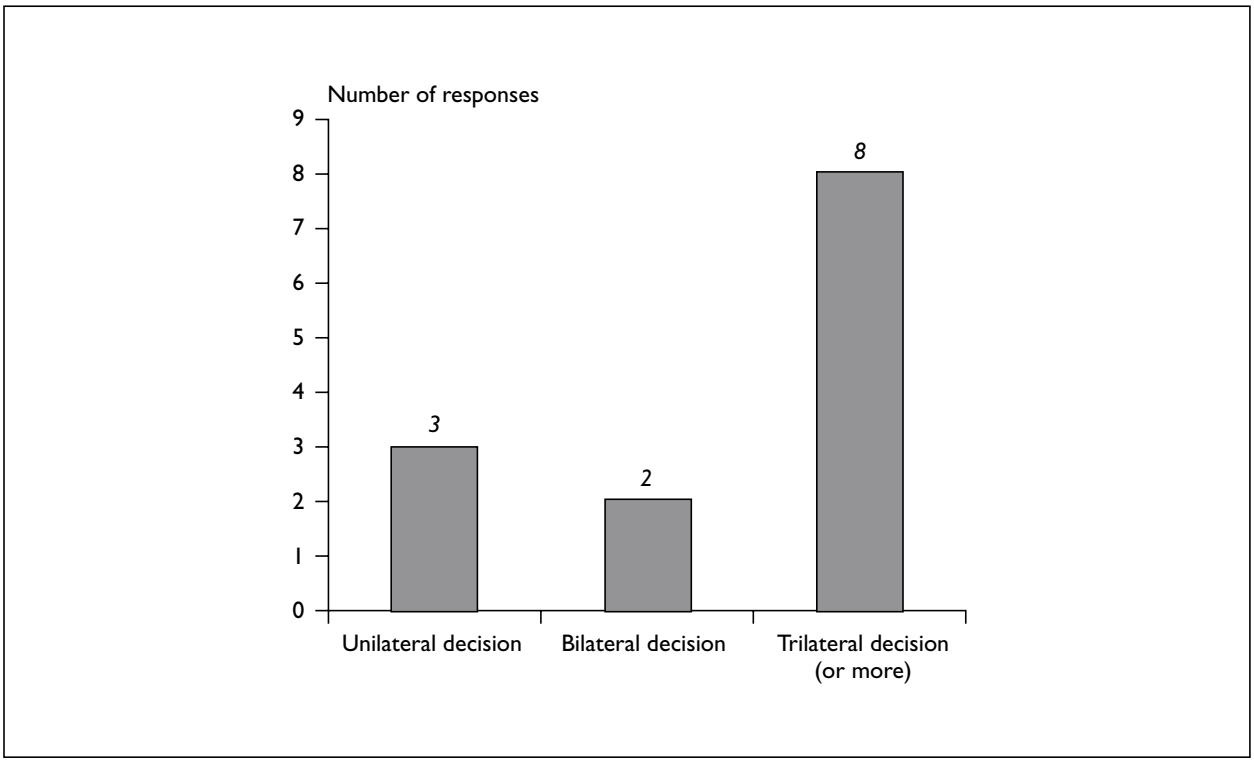

FIGURE 15 *Number of different organisations involved in the decision to start screening – responses of the HAs*

TABLE 30 *Organisations involved in decision to start screening – responses from the prisons, drug services and GUM clinics*

	Prisons (*n* (%))	Drug services (*n* (%))	GUM clinics (*n* (%))
Only your organisation	49 (56)	14 (45)	93 (64)
Your local HA	27 (31)	11 (36)	26 (18)
Missing	2 (2)	0 (0)	7 (5)
GUM organisations	4 (5)	0 (0)	2 (1)
Audit group	0 (0)	0 (0)	1 (1)
Drug services	3 (3)	0 (0)	5 (3)
Prisons	0 (0)	1 (3)	1 (1)
Medical	0 (0)	5 (16)	3 (2)
Patients	0 (0)	0 (0)	2 (1)
Laboratory/pathology/microbiology	1 (1)	0 (0)	5 (3)
Body positive	1 (1)	0 (0)	0 (0)
Healthcare directorate	1 (1)	0 (0)	0 (0)
Total responses	88	31	145

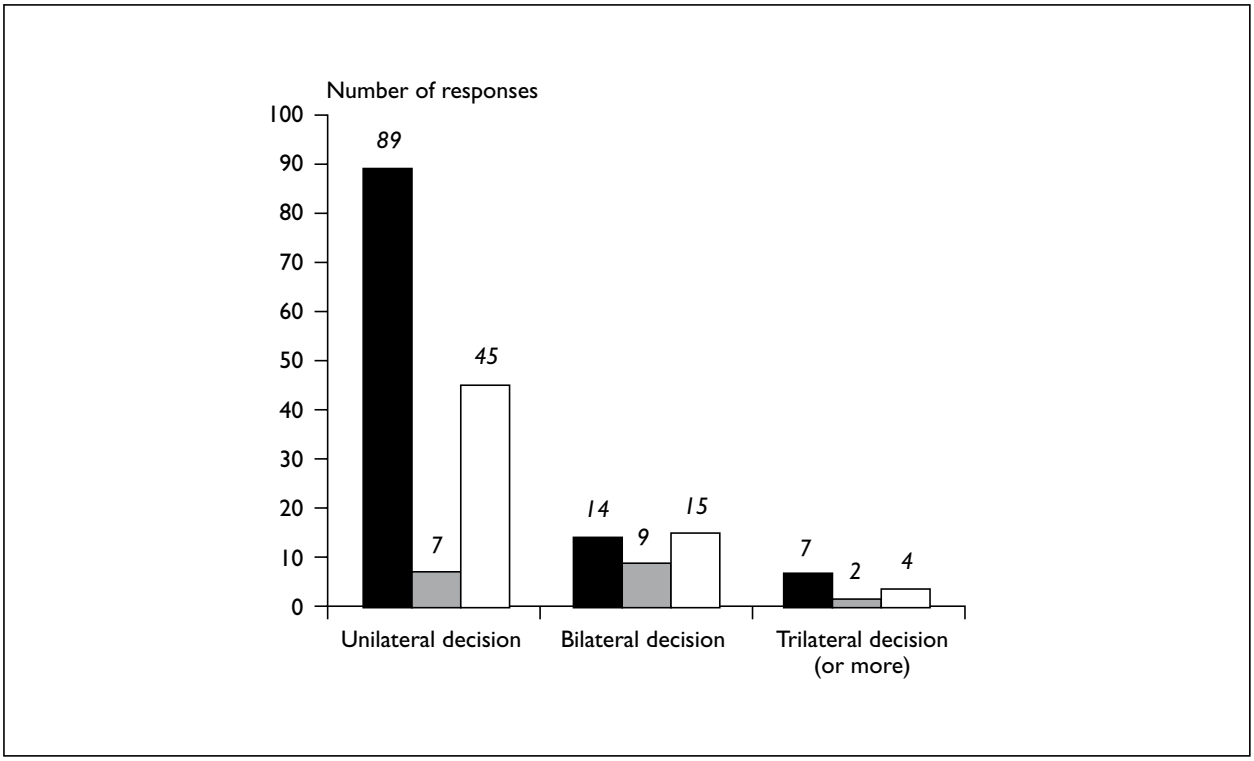

FIGURE 16 *Number of different organisations involved in the decision to start screening – responses of the prisons, drug services and GUM clinics (■, GUM clinics; ▨, drug services; □, prisons)*

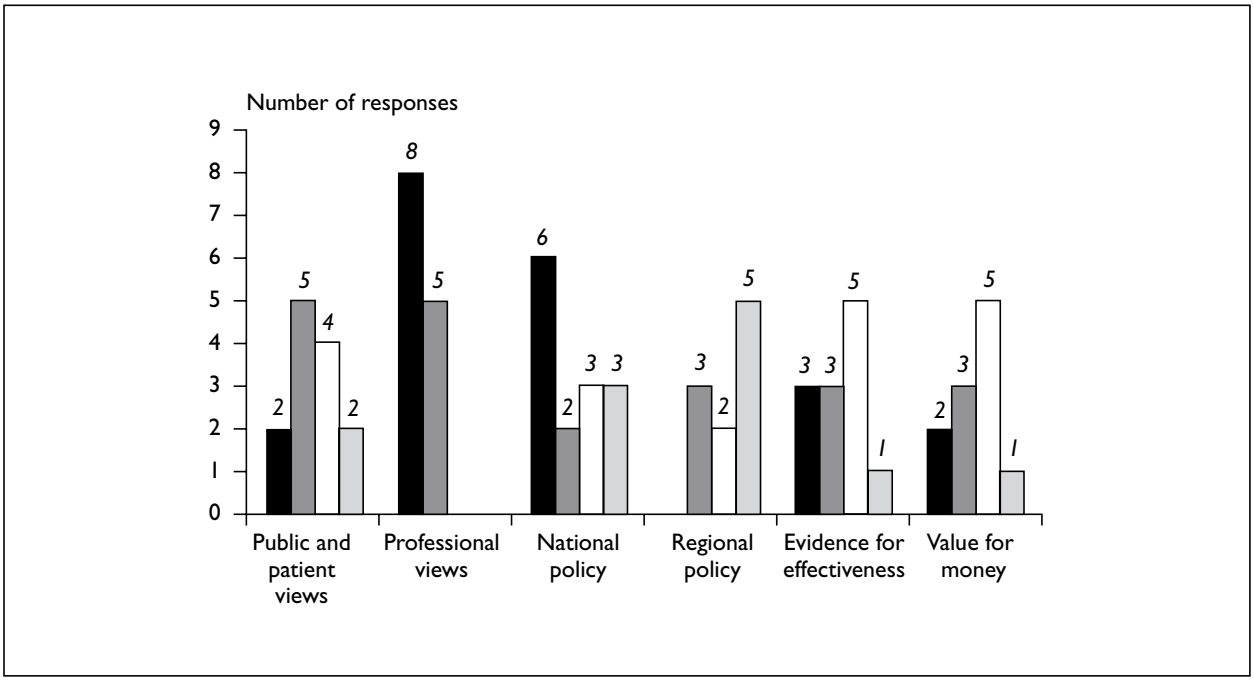

FIGURE 17 *Influences on the decision to start screening – HAs (■,Very influential; ■, moderately influential; □, slightly influential; □, not influential)*

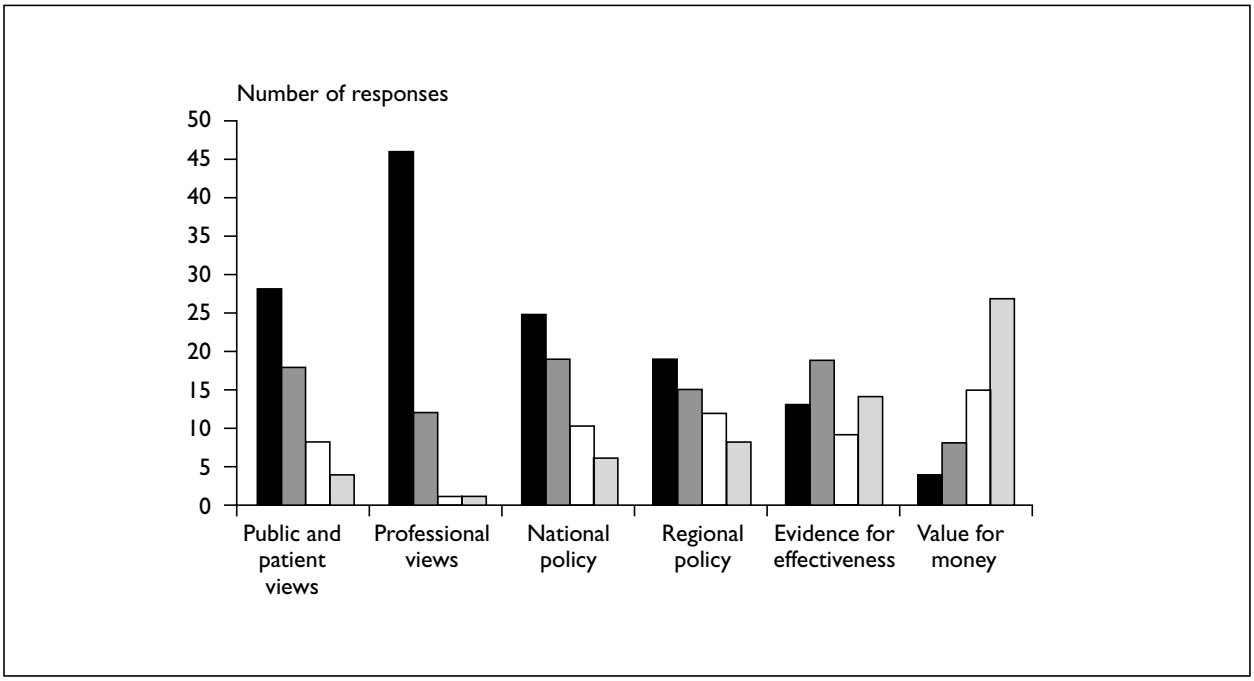

FIGURE 18 *Influences on the decision to start screening – prisons (■,Very influential; ■, moderately influential; □, slightly influential; □, not influential)*

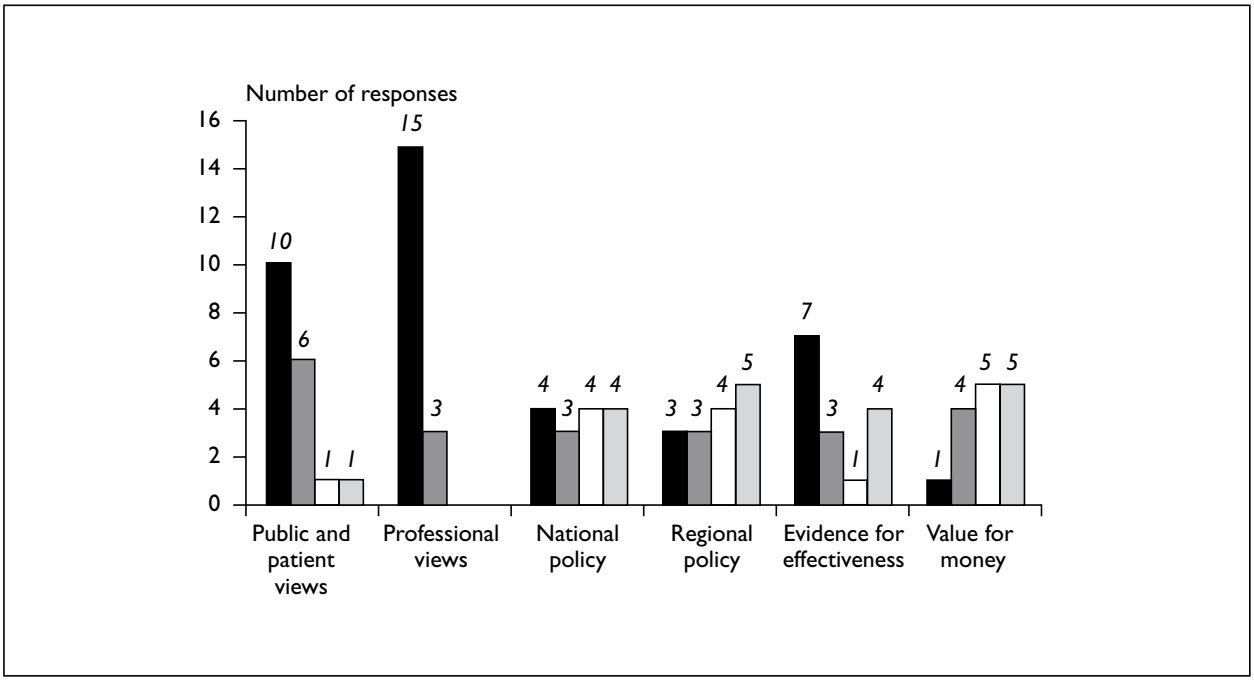

FIGURE 19 *Influences on the decision to start screening – drug services (■, Very influential; ▩, moderately influential; □, slightly influential; ▢, not influential)*

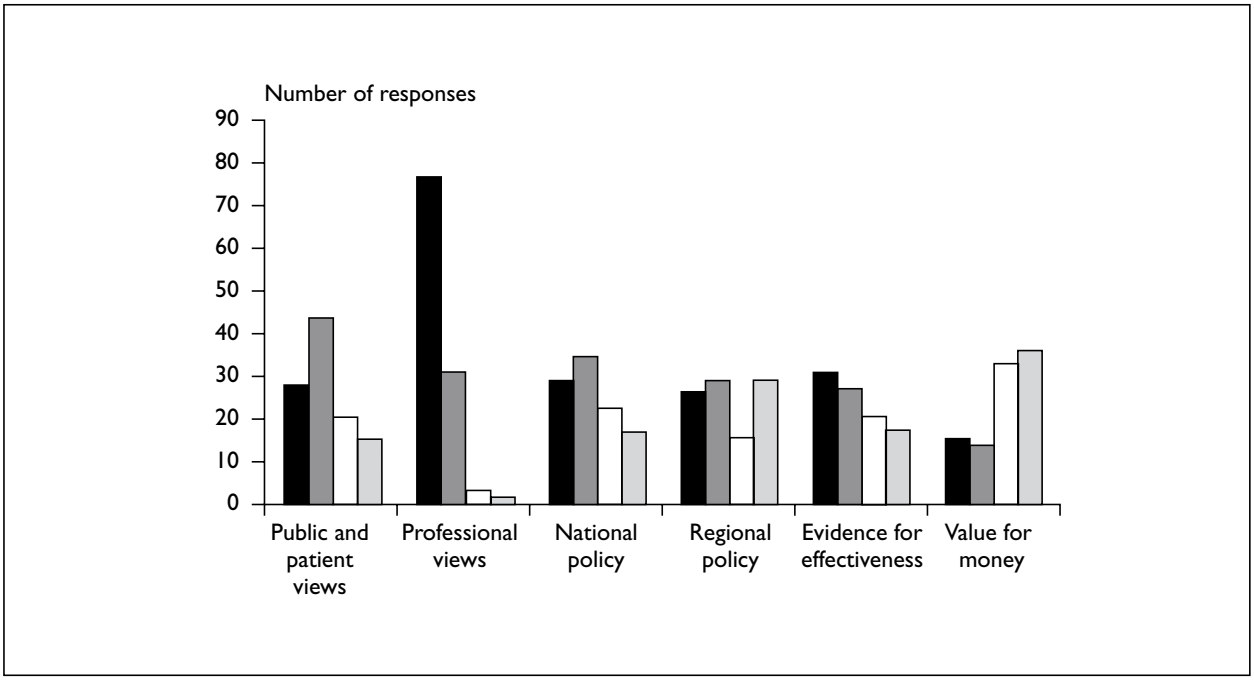

FIGURE 20 *Influences on the decision to start screening – GUM clinics (■, Very influential; ▩, moderately influential; □, slightly influential; ▢, not influential)*

TABLE 31 *Sources of evidence for effectiveness or cost-effectiveness that informed the decision to start screening*

Sources of evidence	HAs (*n* (%))	Prisons (*n* (%))	Drug services (*n* (%))	GUM clinics (*n* (%))
NICE/NHS/Department of Health	2 (20)	2 (8)	1 (17)	2 (6)
Public health	2 (20)	2 (8)	0 (0)	1 (3)
Literature/studies	4 (40)	0 (0)	1 (17)	1 (3)
Experience/opinion/colleagues	1 (10)	1 (4)	0 (0)	10 (31)
Clinicians	0 (0)	2 (8)	1 (17)	0 (0)
HA/Trust	0 (0)	2 (8)	0 (0)	0 (0)
Patients	0 (0)	1 (4)	1 (17)	4 (13)
National guidelines	0 (0)	0 (0)	0 (0)	4 (13)
Audit	0 (0)	0 (0)	1 (17)	1 (3)
Other centres	0 (0)	3 (12)	1 (17)	0 (0)
British Liver Foundation	0 (0)	1 (4)	0 (0)	1 (3)
Centre for Disease Surveillance and Control	1 (10)	0 (0)	0 (0)	0 (0)
Policy	0 (0)	1 (4)	0 (0)	0 (0)
Industry	0 (0)	1 (4)	0 (0)	0 (0)
Microbiology	0 (0)	0 (0)	0 (0)	1 (3)
None	0 (0)	10 (38)	0 (0)	7 (22)
Total responses	10	26	6	32

TABLE 32 *Types of serological tests used to screen for HCV*

Serological tests	HAs (*n* (%))	Prisons (*n* (%))	Drug services (*n* (%))	GUM clinics (*n* (%))
ELISA	6 (32)	14 (21)	4 (22)	47 (38)
ELISA + RIBA	1 (5)	0 (0)	0 (0)	1 (1)
Antibody (non-specified)	5 (26)	25 (38)	6 (33)	47 (38)
Antibody (non-specified) + RIBA	0 (0)	0 (0)	0 (0)	1 (1)
RIBA	0 (0)	0 (0)	1 (6)	1 (1)
Magnetic immunocapture	0 (0)	0 (0)	0 (0)	1 (1)
Not known	2 (11)	13 (20)	5 (28)	10 (8)
Missing	5 (26)	14 (21)	2 (11)	15 (12)
Total number that screen	19	66	18	123

TABLE 33 *Types of virological tests used to screen for HCV*

Virological tests	HAs (*n* (%))	Prisons (*n* (%))	Drug services (*n* (%))	GUM clinics (*n* (%))
PCR	4 (21)	24 (36)	7 (39)	44 (36)
PCR + RIBA	1 (5)	2 (3)	1 (5.5)	5 (4)
RIBA	1 (5)	1 (1)	1 (5.5)	15 (12)
DNA/RNA (non-specified)	1 (5)	2 (3)	0 (0)	7 (6)
Viral load test	0 (0)	0 (0)	0 (0)	1 (1)
Non-interpretable	3 (16)	10 (15)	2 (11)	10 (8)
Not known	1 (5)	3 (5)	1 (5.5)	5 (4)
None	1 (5)	3 (5)	1 (5.5)	2 (2)
Misinterpreted question	0 (0)	4 (6)	2 (11)	8 (7)
Missing	7 (37)	17 (26)	3 (17)	26 (21)
Total number that screen	19	66	18	123

TABLE 34 *Information given to people at the time of screening*

	HAs (*n* (%))	Prisons (*n* (%))	Drug services (*n* (%))	GUM clinics (*n* (%))
Prevention/risks	3 (25)	14 (13)	6 (15)	43 (21)
Counselling	3 (25)	31 (29)	7 (18)	21 (10)
Health/clinical information	1 (8)	5 (5)	2 (5)	5 (2)
Not known	1 (8)	0 (0)	0 (0)	0 (0)
Confidentiality/informed consent/legal	1 (8)	3 (3)	3 (8)	4 (2)
Testing	1 (8)	2 (2)	2 (5)	15 (7)
Disease information	0 (0)	17 (16)	6 (15)	35 (17)
Support available	1 (8)	3 (3)	2 (5)	4 (2)
Treatment	0 (0)	5 (5)	5 (13)	28 (13)
British Liver Foundation information	0 (0)	1 (1)	0 (0)	4 (2)
Leaflets	0 (0)	10 (9)	1 (3)	17 (8)
Notification issues	0 (0)	1 (1)	1 (3)	4 (2)
Implications of a positive test	1 (8)	15 (14)	4 (10)	29 (14)
Total responses	12	107	39	209

TABLE 35 *How organisations inform people of a negative HCV test result*[*]

	HAs (*n* (%))	Prisons (*n* (%))	Drug services (*n* (%))	GUM clinics (*n* (%))
Via GP only	1 (5)	10 (15)	2 (11)	0 (0)
In writing only	0 (0)	2 (3)	0 (0)	1 (1)
On return to the service	9 (47)	26 (39)	11 (61)	70 (57)
Follow-up appointment arranged at time of testing	0 (0)	7 (11)	1 (6)	2 (2)
Contacted to make an appointment when result available	0 (0)	10 (15)	0 (0)	3 (2)
In person	1 (5)	20 (30)	2 (11)	0 (0)
By telephone	0 (0)	0 (0)	0 (0)	7 (6)
Via GP and when return to the service	2 (11)	0 (0)	1 (6)	1 (1)
In person and in writing	0 (0)	1 (2)	1 (6)	0 (0)
Via GP, when return to the service and in writing	0 (0)	1 (2)	0 (0)	1 (1)
When return to the service and in writing	0 (0)	2 (3)	0 (0)	1 (1)
When return to the service or by telephone	0 (0)	0 (0)	0 (0)	35 (28)
When return to the service, in writing or by telephone	0 (0)	0 (0)	0 (0)	3 (2)
Missing	6 (32)	4 (6)	1 (6)	4 (3)
Total number of organisations that screen	19	66	18	123

[*] *Some organisations indicated more than one answer, and, therefore, totals may not add up and percentages may total more than 100%*

TABLE 36 *How organisations inform people of a positive HCV test result*[*]

	HAs (*n* (%))	Prisons (*n* (%))	Drug services (*n* (%))	GUM clinics (*n* (%))
Via GP only	0 (0)	11 (17)	2 (11)	0 (0)
In writing only	0 (0)	1 (2)	0 (0)	0 (0)
On return to the service	8 (42)	28 (42)	11 (61)	95 (77)
Follow-up appointment arranged at time of testing	0 (0)	6 (9)	1 (6)	2 (2)
Contacted to make an appointment when result available	0 (0)	12 (18)	0 (0)	11 (9)
In person	3 (16)	21 (32)	2 (11)	0 (0)
Via GP and when return to the service	2 (11)	1 (2)	1 (6)	3 (2)
In person and in writing	0 (0)	1 (2)	0 (0)	0 (0)
Via GP and in writing	0 (0)	0 (0)	1 (6)	0 (0)
In writing or by telephone	0 (0)	0 (0)	0 (0)	1 (1)
When return to the service and in writing	0 (0)	1 (2)	0 (0)	1 (1)
When return to the service or by telephone	0 (0)	0 (0)	0 (0)	12 (10)
When return to the service, in writing or by telephone	0 (0)	0 (0)	0 (0)	5 (4)
Any/all methods used	0 (0)	0 (0)	0 (0)	2 (2)
Missing	6 (32)	2 (3)	1 (6)	4 (3)
Total number of organisations that screen	19	66	18	123

[*] *Some organisations indicated more than one answer, and, therefore, totals may not add up and percentages may total more than 100%*

TABLE 37 *Treatment available for people with HCV in your area using interferon alone, interferon + ribavirin or pegylated interferon*

Is treatment available in your area?	HAs (*n* (%))	Prisons (*n* (%))	Drug services (*n* (%))	GUM clinics (*n* (%))
Yes	14 (74)	38 (58)	14 (78)	80 (65)
Total responses	19	66	18	123

TABLE 38 *Interferon monotherapy availability*

Is interferon monotherapy available?	HAs (*n* (%))	Prisons (*n* (%))	Drug services (*n* (%))	GUM clinics (*n* (%))
Yes	4 (21)	19 (29)	6 (33)	41 (33)
No	4 (21)	8 (12)	1 (6)	8 (7)
Not known	0 (0)	20 (30)	2 (11)	26 (21)
Missing	11 (58)	19 (29)	9 (50)	48 (39)
Number of organisations that screen	19	66	18	123

TABLE 39 *Interferon plus ribavirin availability*

Is interferon + ribavirin available?	HAs (*n* (%))	Prisons (*n* (%))	Drug services (*n* (%))	GUM clinics (*n* (%))
Yes	14 (74)	32 (48)	11 (61)	70 (57)
No	2 (10)	7 (11)	0 (0)	6 (5)
Not known	0 (0)	17 (26)	1 (6)	30 (24)
Missing	3 (16)	10 (15)	6 (33)	17 (14)
Number of organisations that screen	19	66	18	123

TABLE 40 *Pegylated interferon availability*

Is pegylated interferon available?	HAs (*n* (%))	Prisons (*n* (%))	Drug services (*n* (%))	GUM clinics (*n* (%))
Yes	4 (21)	12 (18)	5 (28)	39 (32)
No	1 (5)	8 (12)	0 (0)	7 (6)
Not known	4 (21)	25 (38)	4 (22)	46 (37)
Missing	10 (53)	21 (32)	9 (50)	31 (25)
Number of organisations that screen	19	66	18	123

TABLE 41 *The proportion of organisations who have eligibility criteria for HCV treatment*

Are there eligibility criteria for treatment?	HAs (*n* (%))	Prisons (*n* (%))	Drug services (*n* (%))	GUM clinics (*n* (%))
Yes	14 (74)	33 (50)	12 (67)	53 (43)
No	0 (0)	2 (3)	0 (0)	6 (5)
Not known	2 (11)	4 (6)	1 (6)	15 (12)
Missing	3 (16)	27 (41)	5 (28)	49 (40)
Number of organisations who screen	19	66	18	123

TABLE 42 *Eligibility criteria for treatment listed by organisations*

Eligibility criteria for treatment	HAs	Prisons	Drug services	GUM clinics
Liver grading/staging	1	11	4	14
Not current IDU/alcohol	3	12	12	20
Absence of mental illness	1	1	1	4
Absence of co-morbidities	1	0	1	1
NICE guidelines	4	0	1	4
Clinical criteria (not specified)	1	1	0	3
Liver function tests	0	7	0	2
Genotype	0	1	0	2
Knodel scoring	0	1	0	1
Age/gender	0	3	0	0
According to clinician	0	6	0	18
Availability of funding	0	2	0	1
Period of custody	0	4	0	0
According to NHS trust/HA/regional centre/ local hospital	0	6	0	12
Co-infection with HIV	0	0	0	1
Interferon-naive or relapsers	0	0	0	1
Compliance	1	1	3	3
Total number of criteria listed	12	56	22	87

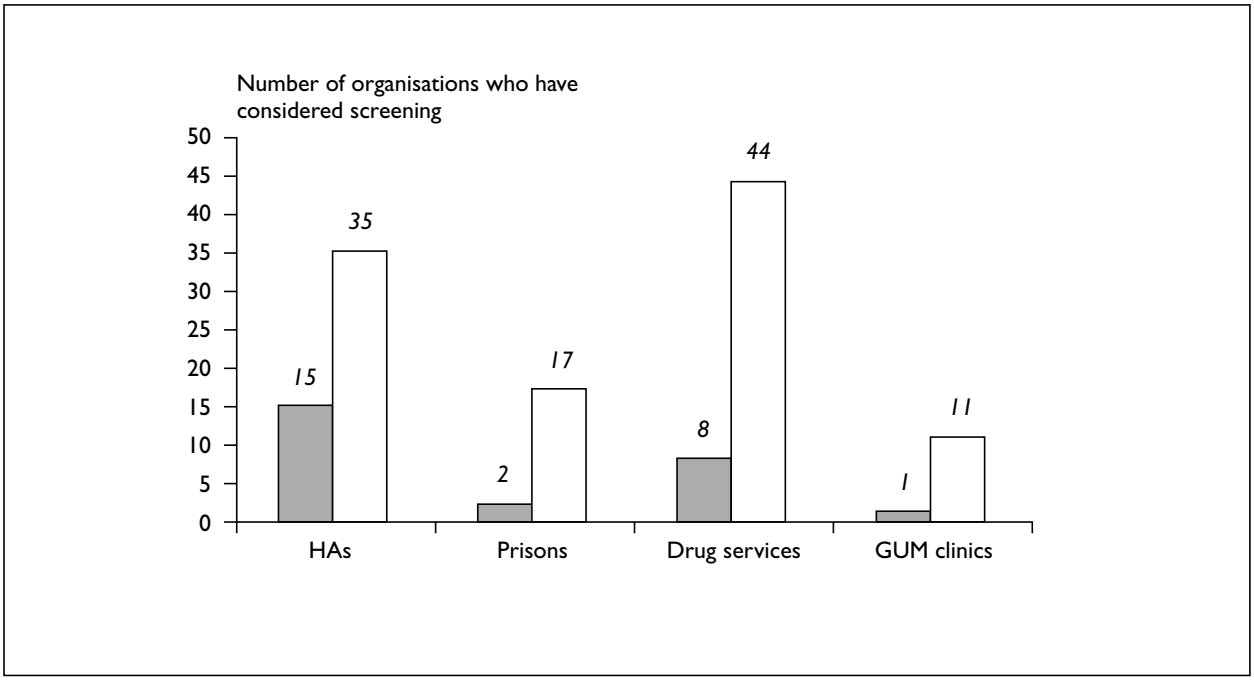

FIGURE 21 *The consideration of screening in those organisations that do not currently screen (■, Yes; □, no)*

TABLE 43 *When the decision was made not to screen for HCV in organisations that do not screen*

	HAs (*n* (%))	Prisons (*n* (%))	Drug services (*n* (%))	GUM clinics (*n* (%))
Continual	3 (20)	0 (0)	0 (0)	0 (0)
Prior to 1998	3 (20)	0 (0)	0 (0)	0 (0)
1999	2 (13)	0 (0)	0 (0)	0 (0)
2000	3 (20)	0 (0)	0 (0)	2 (100)
2001	2 (13)	0 (0)	0 (0)	0 (0)
Currently	2 (13)	0 (0)	0 (0)	0 (0)
Total responses	15	0	0	2

TABLE 44 *Who was involved in the decision not to screen for HCV in organisations that do not screen*

	HAs (*n* (%))	Prisons (*n* (%))	Drug services (*n* (%))	GUM clinics (*n* (%))
Medical staff	6 (18)	1 (50)	2 (33)	1 (100)
Nursing staff	1 (3)	0 (0)	1 (17)	0 (0)
Management	0 (0)	1 (50)	1 (17)	0 (0)
Consultant in Communicable Disease Control	9 (27)	0 (0)	0 (0)	0 (0)
Public Health Department	5 (15)	0 (0)	0 (0)	0 (0)
Drug/mental health workers	7 (21)	0 (0)	2 (33)	0 (0)
HA	3 (9)	0 (0)	0 (0)	0 (0)
Microbiologists	2 (6)	0 (0)	0 (0)	0 (0)
Total responses	33	2	6	1

TABLE 45 *What the influences on the decision not to screen were in organisations that did not screen*

	HAs	Prisons	Drug services	GUM clinics
Public and patient				
Very influential	0	0	2	0
Moderately influential	1	0	0	1
Slightly influential	3	0	1	0
Not influential	1	0	1	1
Professional				
Very influential	4	0	1	2
Moderately influential	3	0	2	0
Slightly influential	2	0	0	0
Not influential	0	0	1	0
National policy				
Very influential	4	0	1	1
Moderately influential	1	0	1	0
Slightly influential	1	0	0	1
Not influential	1	0	2	0
Regional policy				
Very influential	5	0	2	1
Moderately influential	0	0	1	0
Slightly influential	0	0	0	0
Not influential	2	0	1	0
Effectiveness				
Very influential	2	0	0	0
Moderately influential	3	0	1	1
Slightly influential	1	0	1	0
Not influential	0	0	2	1
Value for money				
Very influential	2	0	0	0
Moderately influential	4	0	1	1
Slightly influential	0	0	0	0
Not influential	1	0	3	0

Appendix 5

Effectiveness of treatments for HCV

Ribavirin + interferon-α combination therapy

The systematic review conducted to inform the guidance on combination therapy issued by NICE included 19 RCTs and two meta-analyses.[78] Results confirmed that combination therapy produces larger sustained virological response rates than monotherapy (see *Table 13*).

NICE recommended that 6 months of combination therapy is appropriate as first-line treatment or following failure of interferon-α monotherapy. The review[78] advised that at 6 months, continuation of treatment should depend on factors that may predict a good sustained response.

One additional meta-analysis[82] and one systematic review[83] were identified. The meta-analysis[82] assessed the effectiveness of combination therapy compared to interferon-α monotherapy as first-line treatment in relapsers and non-responders with HCV and reported a sustained virological response of 24% with combination therapy. The review by Kjaergard and colleagues[83] included the same patient groups and concluded that, compared with interferon-α monotherapy, combination therapy reduced the risk of no virological response by 28% at a median of 24 weeks in interferon-naive patients (relative risk = 0.72, 95% CI, 0.65 to 0.79) and 33% in relapsers (relative risk = 0.67, 95% CI, 0.57 to 0.78). Both of these studies were of high quality and confirmed the findings and conclusions of the previous assessment.[78]

Another two recent meta-analyses[126,127] reported virological response rates of combination therapy compared to interferon monotherapy in patients who failed first-line interferon treatment, which is beyond the scope of this review. No more additional relevant RCTs were identified that have been published since the Shepherd and colleagues review.[78]

The results from the Shepherd and colleagues assessment[78] of therapy for HCV were used as the base estimates due to the appropriateness to the UK setting, the similar population of HCV patients being studied and the high methodological quality of the review. There was a range of assumptions (including transition probabilities) in the economic HCV therapy model of cost-effectiveness, and in the current economic model the assumptions follow those reported by Shepherd and colleagues.[78]

Pegylated interferon in combination therapy

The addition of a polyethyleneglycol molecule to interferon (pegylated interferon) produces a molecule with a longer half-life and more favourable pharmacokinetics (such as more sustained absorption, reduced clearance and a smaller volume of distribution).[116,117] These characteristics give the advantage of a once per week injection compared to three times per week for non-pegylated interferon-<Gk a>. Pegylated interferon is commonly used in practice in combination with ribavirin.

Seven recent RCTs[116,117, 128–132] were identified comparing pegylated interferon-α to interferon-α alone. Two studies were excluded due to having small patient numbers (both < 100) and due to difficulty in locating the papers.[131,132] Only the RCT by Mann and colleagues reported the use of pegylated interferon in combination with ribavirin, and, therefore, these study results have been used.[116]

Pegylated interferon was administered once a week and interferon-α was administered three times per week. Study quality was high, the method of randomisation was stated and randomisation was concealed. The study was single-blinded and had clear inclusion and exclusion criteria. All patients that were enrolled in the study were accounted for and the analysis was performed on an intention-to-treat basis. The patients in each group had similar baseline characteristics and patients were treated equally in ways other than the intervention. A sample size calculation was performed. The virological response was reported at the conclusion of follow-up (24 weeks after the end of therapy; see *Table 46*).

As pegylated interferon is not yet recognised as standard treatment and evidence is still

TABLE 46 *Virological response rate to pegylated interferon*[116]

Study	Patients	Treatment	Comparator	Efficacy – virological response
Manns *et al.*, 2001[116]	HCV with no previous interferon treatment (*n* = 1530)	(A) Pegylated interferon-α2b + ribavirin (800 mg/day) (B) Pegylated interferon-α2b + ribavirin (1000–1200 mg/day)	Interferon-α2b (3 mega units) + ribavirin (1000–1200 mg/day)	Pegylated interferon 1.5 μg/kg: 54% Pegylated interferon 0.5 μg/kg: 47% Interferon: 47%

emerging, estimates for response rates of pegylated combination treatment were not used in the base case. However, for illustration, the cost–utility of screening assuming 100% use of pegylated interferon was calculated in the Results of the CUA section of the results chapter.

Appendix 6

Cost-effectiveness of screening: sensitivity analyses

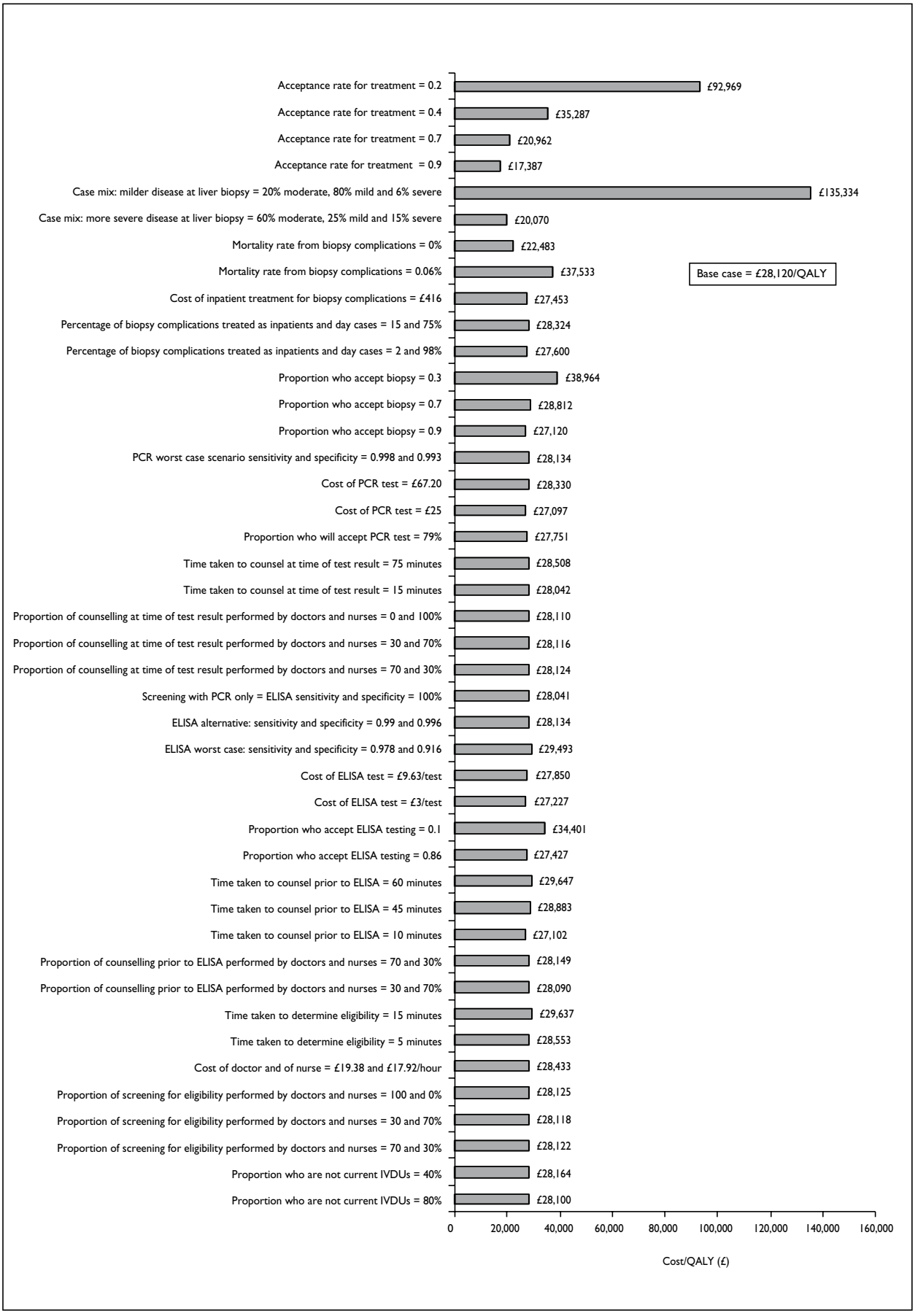

FIGURE 22 *Drug services sensitivity analyses results – screening assumptions*

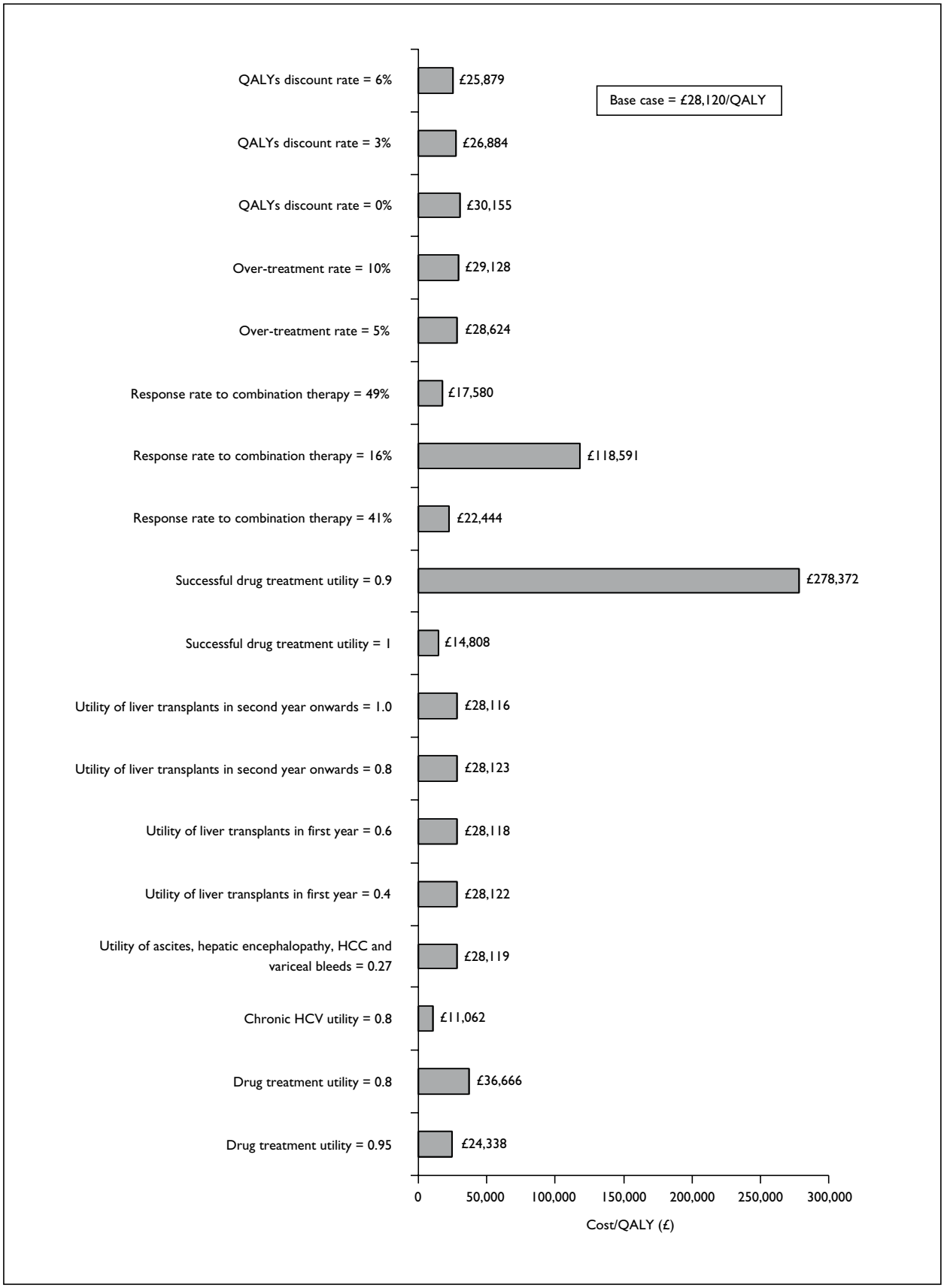

FIGURE 23 *Drug services sensitivity analyses results – treatment assumptions*

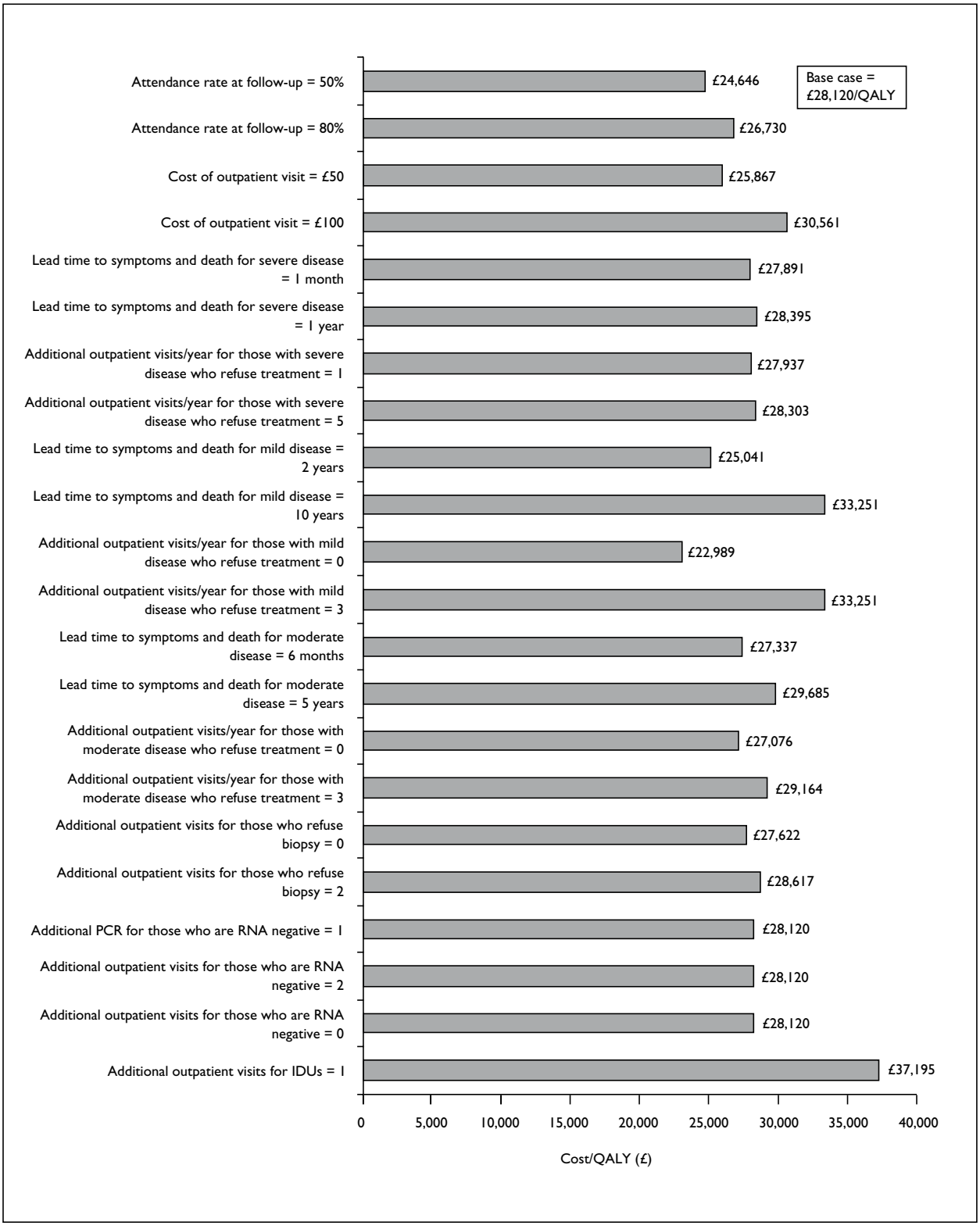

FIGURE 24 *Drug services sensitivity analyses results – follow-up assumptions*

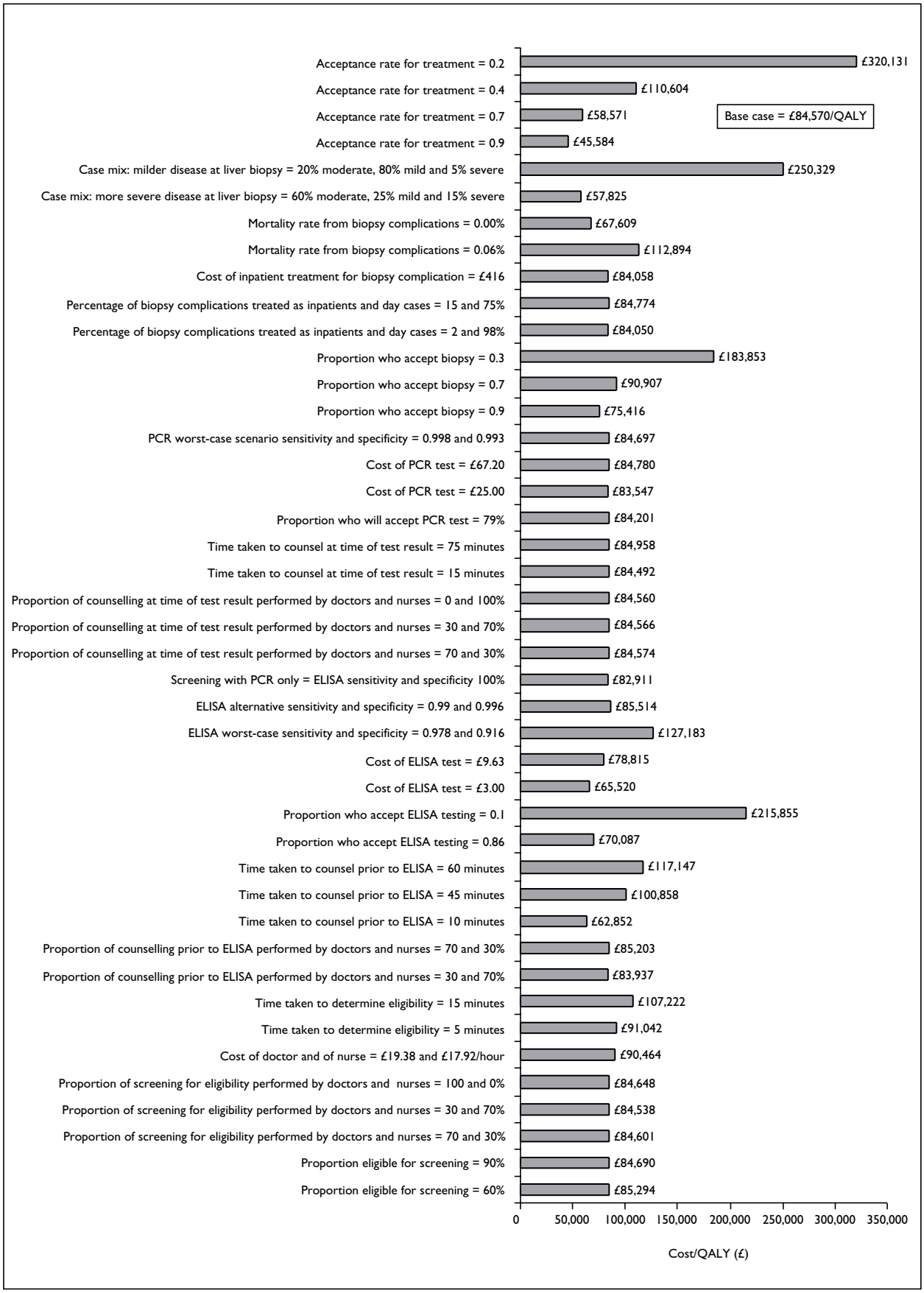

FIGURE 25 *GUM clinics sensitivity analyses results – screening assumptions*

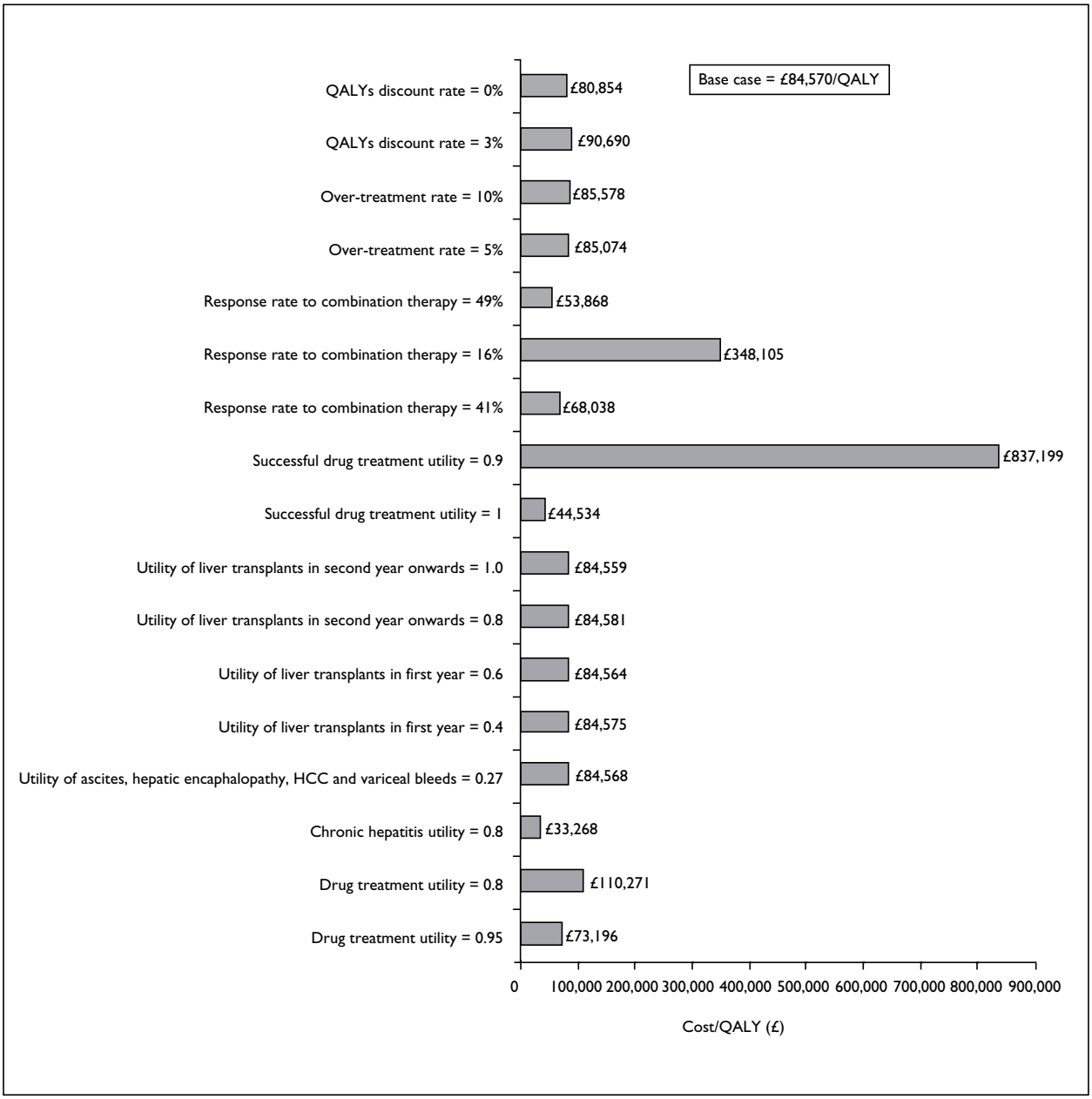

FIGURE 26 *GUM clinics sensitivity analyses results – treatment assumptions*

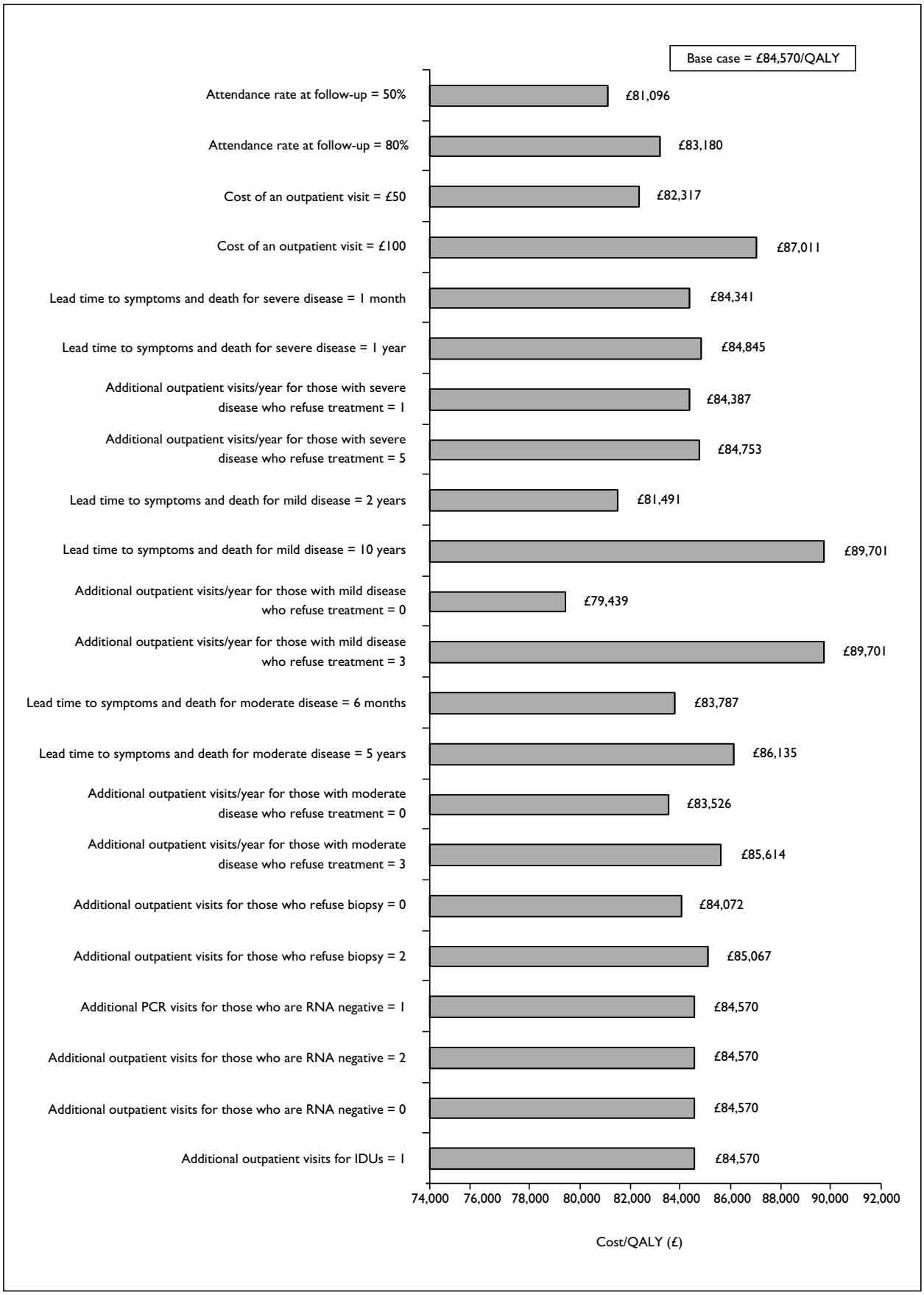

FIGURE 27 *GUM clinics sensitivity analyses results – follow-up assumptions*

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We look forward to hearing from you.

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