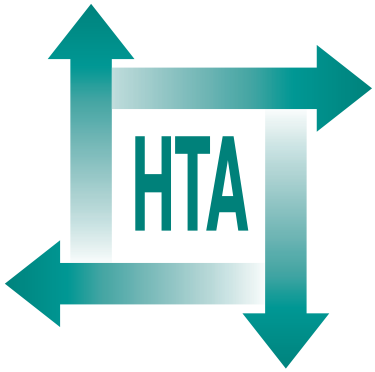
Health Technology Assessment 2007; Vol. 11: No. 11

Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation

J Shepherd, J Jones, D Hartwell, P Davidson, A Price and N Waugh

March 2007

Health Technology Assessment
NHS R&D HTA Programme
www.hta.ac.uk



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

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

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

You can order HTA monographs from our Despatch Agents:

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

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

Contact details are as follows:

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

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

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

Payment methods

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

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

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

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

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

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

Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation

J Shepherd,[1*] J Jones,[1] D Hartwell,[1] P Davidson,[1] A Price[1] and N Waugh[2]

[1] Southampton Health Technology Assessments Centre, UK
[2] Department of Public Health, University of Aberdeen, UK

* Corresponding author

Declared competing interests of authors: P Davidson is a member of the editorial board for *Health Technology Assessment*, but he was not involved in the editorial process for this report

Published March 2007

This report should be referenced as follows:

Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess* 2007;**11**(11).

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

NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) Programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Secondly, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Thirdly, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer-reviewed by a number of independent expert referees before publication in the widely read monograph series *Health Technology Assessment*.

Criteria for inclusion in the HTA monograph series

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

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

The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 04/49/01. The protocol was agreed in February 2005. The assessment report began editorial review in March 2006 and was accepted for publication in June 2006. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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

ISSN 1366-5278

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

T

Abstract

Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation

J Shepherd,[1*] J Jones,[1] D Hartwell,[1] P Davidson,[1] A Price[1] and N Waugh[2]

[1] Southampton Health Technology Assessments Centre, UK
[2] Department of Public Health, University of Aberdeen, UK
* Corresponding author

Objectives: To assess the clinical effectiveness and cost-effectiveness of pegylated interferon alfa (PEG) and non-pegylated interferon alfa (IFN) and ribavirin (RBV) for the treatment of adults with histologically mild chronic hepatitis C (HCV) infection.
Data sources: Electronic bibliographic databases were searched up to July 2005.
Review methods: A systematic review and an economic evaluation were carried out. A Markov state transition model was developed to estimate the cost-effectiveness of treatment strategies for adults with mild chronic HCV.
Results: Among the included studies, eight randomised controlled trials (RCTs) of antiviral treatment in mild HCV were identified and included. In general these RCTs were of good quality. The results suggested that effectiveness, particularly with respect to sustained virological response was similar in patients with mild disease to the results obtained in patients with moderate/severe disease. This finding was supported by RCTs reporting the results for mild HCV sub-groups. The authors' cost-effectiveness analysis showed that early treatment compared with watchful waiting is associated with quality-adjusted life-year (QALY) gains but with increased treatment costs. The base-case incremental costs per QALY for 48 weeks of treatment are: watchful waiting with IFN + RBV versus best supportive care = £3097–6585; early treatment with IFN + RBV versus watchful waiting with IFN + RBV = £5043–8092; watchful waiting with PEG 2a + RBV versus best supportive care = £3052; early treatment with PEG 2a + RBV versus watchful waiting with PEG 2a + RBV = £5900; watchful waiting with PEG 2b + RBV versus best supportive care = £2534; and early treatment with PEG 2b + RBV versus watchful waiting with PEG 2b + RBV = £5774. These results were consistent with previous assessments of cost-effectiveness.
Conclusion: This systematic review and economic evaluation show that patients with histologically mild HCV can be successfully treated with both pegylated and non-pegylated interferon alfa. Early treatment and watchful waiting strategies are associated with acceptable cost-per-QALY estimates. Research needs to be directed towards newer, potentially more effective interventions, particularly those that improve treatment response in patients with genotype 1, with minimal adverse effects. Further research is required into the natural history of HCV to estimate better the rate of liver disease progression, and also into the effectiveness of non-invasive biochemical markers of liver disease, as an alternative to liver biopsy.

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

α-Fetoprotein (AFP) A protein substance normally produced by the liver. Measurement of AFP in the bloodstream can be used as an early detection test for hepatocellular carcinoma.

Alanine aminotransferase An enzyme that indicates liver inflammation.

Ascites Large accumulation of fluid in the abdominal cavity.

Biochemical response Normalisation of alanine aminotransferase levels often defined as <40 IU/l.

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 or regenerating cells.

Compensated liver disease Compensation is the act of making up for a functional or structural deficiency. For example, compensation for the loss of a diseased kidney is brought about by an increase in size of the remaining kidney, so restoring the urine-producing capacity.

Decompensated liver disease The phase of progressive disease whereby the liver is no longer able to account for damage caused by scarring (fibrosis) and inflammation. Ascites, variceal haemorrhage and hepatic encephalopathy are complications that can occur during decompensation.

Early virological response (EVR) Fall in HCV RNA by at least 2 log 10 units or to an undetectable level at week 12 of treatment.

Fibrosis Thickening and scarring of connective tissue, most often a consequence of inflammation or injury.

Hepatitis C virus ribonucleic acid (HCV RNA) Genetic material that indicates the replication of the virus and therefore persistence of infection.

Histological response Defined as a decrease of at least 2 points in the total score on the Ishak Histological Activity Index, where a score of 0 indicates no inflammatory changes and no fibrosis and a score of 22 indicates multilobular necrosis, marked intralobular degeneration and focal necrosis, marked portal inflammation and cirrhosis.

Human immunodeficiency virus (HIV) Recognised as the agent that induces AIDS.

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

METAVIR A scoring system for hepatic inflammation and fibrosis (from 0 to 4).

Non-response Patients who do not show evidence of clearing the hepatitis C virus either during treatment or after the cessation of treatment.

Polymerase chain reaction (PCR) A sensitive technique of molecular genetics in which the DNA of a single cell treatment polymerase enzyme is induced to replicate many times. This enables the DNA to be amplified in sufficient quantities to permit generic analysis. A negative PCR indicates absence of virus in the blood and is one indication of treatment response.

continued

Glossary *continued*

Relapse Patients who have shown evidence of having cleared the hepatitis C virus during treatment, but who did not maintain a sustained virological response, i.e. the virus became detectable again within the follow-up period.

Sustained complete response (SR) Both a biochemical and virological response to treatment, sustained after treatment generally measured 24 weeks after treatment ends.

Sustained virological response (SVR) Often defined as HCV RNA <100 copies/ml that is maintained after treatment cessation usually measured 24 weeks after treatment stops.

Transcription-mediated amplification (TMA) TMA can detect residual levels of virus less than 50 HCV RNA copies.

Viral load The amount of HCV RNA present in the body.

Viraemia The presence in the blood of virus.

Virological response Absence of HCV RNA on polymerase chain reaction.

List of abbreviations

ALT	alanine aminotransferase
BNF	British National Formulary
BSG	British Society of Gastroenterology
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CRD	NHS Centre for Reviews and Dissemination
CT	computed tomography
DNA	deoxyribonucleic acid
DoH	Department of Health
EuroQol	also known as the EQ-5D instrument, used to estimate a patient's quality of life
EVR	early virological response
FBC	full blood count
FSS	Fatigue Severity Scale
HAI	Histological Activity Index
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HE	hepatic encephalopathy
HIV	human immunodeficiency virus
HPA	Health Protection Agency
HRQoL	health-related quality of life
HTA	health technology assessment
HUI	Health Utility Index
ICER	incremental cost-effectiveness ratio
IDU	injecting drug user

continued

List of abbreviations *continued*

IFN	non-pegylated interferon alfa (either 2a or 2b)
IFN + RBV	non-pegylated interferon and ribavirin given in combination during the same period
ITT	intention-to-treat
MCHN	Managed Clinical Hepatology Network
MCS	mental component score
MU	million international units
NICE	National Institute for Health and Clinical Excellence
NPV	negative predictive value
NS	not statistically significant
OR	odds ratio
PCR	polymerase chain reaction
PCS	physical component score
PEG	pegylated interferon alfa (either 2a or 2b)
PNALT	persistently normal alanine aminotransferase
PPV	positive predictive value
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RBV	ribavirin
RCT	randomised controlled trial
RNA	ribonucleic acid
RR	relative risk
SD	standard deviation
SF-36	Short Form with 36 Items
SG	standard gamble
SHTAC	Southampton Health Technology Assessments Centre
SR	sustained response
SUHT	Southampton University Hospitals Trust
SVR	sustained virological response
TFT	thyroid function tests
TTO	time trade-off
U&E	urea and electrolytes
ULN	upper limit of normal
VAS	visual analogue scale
WHO	World Health Organization

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

Executive summary

Objective

The aim of this systematic review and economic evaluation is to assess the clinical effectiveness and cost-effectiveness of pegylated interferon alfa (PEG) and non-pegylated interferon alfa (IFN) and ribavirin (RBV) for the treatment of adults with histologically mild chronic hepatitis C infection.

Epidemiology and background

Hepatitis C virus (HCV) is a blood-borne virus that can be transmitted by infected blood or blood products, via blood transfusion or clotting factors (as used in haemophilia) and contaminated hypodermic needles. It is estimated that between 200,000 and 400,000 people may be chronically infected in the UK, the majority of whom are male. Estimates of the proportion of infections that could be considered mild vary, but could be as high as 85%. Because of shared routes of transmission, a proportion of those infected with HCV are also co-infected with HIV and hepatitis B virus (HBV). It is estimated that around 1800 people with haemophilia are living with chronic HCV infection.

After exposure, up to 80% of people develop chronic infection. Disease progression is variable, occurring over a 20–50-year period. Although some people may never progress, around 30% will develop liver cirrhosis over a 20–30-year period. The severity of disease is established via liver biopsy, with fibrosis scores of 0–2 generally indicating milder disease (depending on which classification system is used).

Currently, patients who present with histologically mild HCV are monitored with repeat biopsies every few years. Antiviral treatment is only initiated when fibrosis and inflammation levels are indicative of moderate to severe disease. The National Institute for Health and Clinical Excellence (NICE) has previously issued guidance on the use of antiviral treatment in moderate to severe HCV; however, antiviral treatment in patients with histologically mild HCV has not been assessed at a policy level before. This assessment therefore compares treatment of patients early on, when liver disease is mild, with a policy of 'watchful waiting' whereby treatment is offered when the infection has advanced.

Methods

A systematic review and an economic evaluation were conducted. A sensitive search strategy was designed and applied to a number of electronic bibliographic databases up to July 2005. Manufacturer and sponsor submissions to NICE were also searched. The trials were reviewed in a narrative synthesis, but meta-analysis was not undertaken due to heterogeneity in the interventions and comparators evaluated.

A Markov state transition model was developed to estimate the cost-effectiveness of treatment strategies for adults with mild chronic HCV, from the perspective of the NHS and personal social services. The model includes eight health states through which a cohort of patients pass at different rates. A lifetime horizon was employed, with a cycle length of 1 year. Published quality of life weights were taken from a UK randomised control trial (RCT) in order to derive quality-adjusted life-years (QALYs). Transition rates through the health states were estimated from published literature, including the UK RCT. Costs and resources were estimated from published literature and clinical opinion.The cost year was 2003–4. Costs were discounted at 6% and benefits at 1.5%.

Uncertainty in assumptions and parameters was investigated through probabilistic and deterministic sensitivity analyses.

Results

Clinical effectiveness results

Virological response

In two PEG RCTs, treatment for 48 weeks with PEG 2a + RBV was significantly more effective than the same treatment for 24 weeks [sustained

virological response (SVR) at 48 weeks, range 52–63%]. In the third PEG trial, treatment with PEG + RBV resulted in a significantly higher SVR than treatment with IFN + RBV. All five IFN trials reported significantly higher SVR rates with IFN + RBV (range 33–69%) compared with either IFN monotherapy (range 18–23%) or no treatment (zero response).

All eight trials reported SVRs for subgroups of patients according to different prognostic and demographic factors. Logistic regression analysis was also performed to examine the independent effect of these factors on virological response.

In the three PEG 2a + RBV trials, higher SVRs were seen in genotype non-1 patients compared with genotype 1 patients, regardless of length of therapy. Genotype 1 patients treated with PEG + RBV for 48 weeks had significantly higher response rates than patients on the same therapy for only 24 weeks. Treatment duration did not have a significant effect on virological response for patients with genotype 2 or 3.

Patients with genotype 1 and low baseline viral load treated for 48 weeks had significantly higher SVRs than genotype 1 patients with high baseline viral load. In patients with genotypes 2 or 3, there was little additional benefit in extending treatment to 48 weeks, regardless of viral load.
Patients with genotype non-1 aged 40 years or younger had a 26% higher probability of achieving an SVR compared with patients who were older than 40 years (relative risk 1.26; 95% confidence interval 1.02 to 1.55). One trial reported results for subgroups of patients with varying stages of fibrosis. In general, SVRs were higher in patients with mild HCV (fibrosis score F0 or F1, scored using the Knodell system) compared with those with bridging fibrosis/cirrhosis (F3 or F4) (it was not reported whether this difference was statistically significant). In mild HCV patients with genotypes 2 or 3, there was a small net loss of benefit when treatment was extended to 48 weeks.

No RCTs of the other pegylated interferon alfa, PEG 2b, in patients with mild HCV met the inclusion criteria. However, a large multi-centre international RCT of PEG 2b + RBV in patients with moderate to severe HCV reported subgroup analyses based on fibrosis stage. For patients with no or minimal fibrosis treated with the standard dose of PEG 2b + RBV for 48 weeks, SVRs were in the range 54–61%, depending on RBV dose. For patients with bridging fibrosis/cirrhosis, SVRs were in the range 39–55%.

In the five IFN + RBV trials, SVRs were higher for patients with non-1 genotypes compared with genotype 1 in all trials. In two RCTs, within-group differences were statistically significant ($p \leq 0.05$). In one RCT, SVRs were significantly higher for patients with low baseline viraemia in both the dual therapy treatment group (92 vs 46%, $p < 0.05$) and monotherapy treatment group (50 vs 0%, $p < 0.005$). The baseline histological staging (scored using the Scheuer criteria) significantly affected the SVR within the combination therapy group of one trial. SVRs for patients with a lower fibrosis stage (F0 or F1) were more than twice that of patients with a higher fibrosis stage (F >1) (63 vs 28%, respectively, $p = 0.004$). Differences in SVR according to age >40 years or <40 years (measured in two trials), or normal or raised baseline alanine aminotransferase levels (one trial), were not significant.

Health-related quality of life (HRQoL)

Published data on HRQoL were available for only one of the RCTs (comparing IFN + RBV versus no treatment) using the Short Form with 36 Items (SF-36). At 24 weeks after the end of treatment, there was a mean improvement from baseline in seven out of eight of the SF-36 subscales in patients with an SVR. Significant improvement was reported for bodily pain, general health and vitality ($p = 0.01$ compared with controls). Mean improvements were also observed in five of eight subscales in treatment failures (non-responders and relapsed patients).

The impact of PEG 2a + RBV on HRQoL is currently available only in a conference abstract. SF-36 and Fatigue Severity Scale scores were better for patients achieving an SVR than non-responders or untreated controls.

Adverse events

The trials varied substantially in the detail of their reporting of adverse events. However, the most frequently occurring adverse events were the same in all eight RCTs, and included influenza-like symptoms such as headache, fatigue, fever and myalgia. Depression also occurred fairly commonly. Overall, the incidence of adverse events did not differ greatly between treatment groups for all the trials, although in two trials the incidence was higher in the treatment groups compared to no treatment, as would be expected. Two trials reported statistical tests for comparisons between groups.

The incidence of any dose discontinuations due to adverse events was reported by all eight trials and

was similar across treatment groups (range 8–17%) for the five IFN trials and one PEG trial. For the other two PEG trials, there was larger variation between treatment groups (range 7–57%). In both studies, the highest proportion of patients who had to stop treatment due to adverse events occurred in those receiving PEG + RBV for the longer duration of 48 weeks (range 18–57%), and was two to four times the incidence in patients receiving the same treatment for 24 weeks (range 7–12%).

Monotherapy

The two PEG monotherapy trials containing predominantly mild HCV patients reported SVRs of up to 30%, depending on PEG formulation and dose.

Subgroups of mild and moderate to severe patients

In general, higher SVRs were observed for patients classified as having mild fibrosis at baseline, compared with those classified as advanced fibrosis/cirrhosis (n= 7 studies). However, this was statistically significant in only one study, with the remaining studies not reporting any significance values. In five studies, no or minimal fibrosis was significantly and independently associated with SVR, as assessed in multivariate logistic regression analyses.

Cost-effectiveness results

Systematic review of cost-effectiveness studies

All six selected studies indicate that antiviral treatment is effective in terms of improved life expectancy and quality-adjusted life expectancy compared with no antiviral treatment. Those studies which compared the effects of immediate versus delayed treatment (i.e. watchful waiting) generally showed that early intervention is cost-effective for genotype non-1 patients, but less so for genotype 1 patients.

Authors' cost-effectiveness analysis

The base case incremental costs per QALY for 48 weeks of treatment are as follows:

- watchful waiting with IFN + RBV versus best supportive care = £3097–6585
- early treatment with IFN + RBV versus watchful waiting with IFN + RBV = £5043–8092
- watchful waiting with PEG 2a + RBV versus best supportive care = £3052
- early treatment with PEG 2a + RBV versus watchful waiting with PEG 2a + RBV = £5900
- watchful waiting with PEG 2b + RBV versus best supportive care = £2534
- early treatment with PEG 2b + RBV versus watchful waiting with PEG 2b + RBV = £5774.

Early treatment compared with watchful waiting is associated with QALY gains and increased treatment costs. Cost per QALY estimates are therefore higher than watchful waiting compared with best supportive care. Early treatment involves providing interferon dual therapy to all patients with mild disease, some of whom will never progress to the moderate to severe stage. In contrast, the watchful waiting strategy involves providing antiviral treatment only to those patients where disease progresses. Moreover, early treatment means that drug costs and excess costs for monitoring patients are all incurred in the first year of the strategy, rather than at a future date determined by the rate of disease progression.

For genotype 1 patients the incremental costs per QALY for 48 weeks of treatment are as follows:

- watchful waiting with IFN + RBV versus best supportive care = £7766–19,022
- early treatment with IFN + RBV versus watchful waiting with IFN + RBV = £9021–15,954
- watchful waiting with PEG 2a + RBV versus best supportive care = £6867
- early treatment with PEG 2a + RBV versus watchful waiting with PEG 2a + RBV = £10,270
- watchful waiting with PEG 2b + RBV versus best supportive care = £4670
- early treatment with PEG 2b + RBV versus watchful waiting with PEG 2b + RBV = £8324.

For genotype non-1 patients the incremental costs per QALY for 48 weeks of treatment are as follows:

- watchful waiting with IFN + RBV versus best supportive care = £1558–3105
- early treatment with IFN + RBV versus watchful waiting with IFN + RBV = £3528–5050
- watchful waiting with PEG 2a + RBV versus best supportive care = £1326
- early treatment with PEG 2a + RBV versus watchful waiting with PEG 2a + RBV = £3725
- watchful waiting with PEG 2b + RBV versus best supportive care = £1387
- early treatment with PEG 2b + RBV versus watchful waiting with PEG 2b + RBV = £4320.

Comparisons are also made between PEG and IFN, in terms of early versus early treatment, and delayed versus delayed treatment. Results vary according to which PEG is used (2a or 2b), and the SVR.

When applying early stopping rules for patients not demonstrating a viral response after 12 weeks, costs for the watchful waiting strategies typically reduce by around £700 and for early treatment fall by around £3000. There is less of an impact in terms of QALYs. Early stopping strategies are also modelled according to genotype. The order of reduction in lifetime costs is slightly lower for genotype 1 patients than for the mixed cohort of genotype 1 and genotype non-1. The greatest reductions in cost are realised by applying a 24-week duration of treatment to genotype non-1 patients. Costs for watchful waiting reduce by approximately £1000 and for early treatment by approximately £4000.

A number of scenarios to explore differences in SVR for IFN compared with PEG were conducted. The SVRs for PEG used in the model were replaced by lower values. These were based on the SVR reported for IFN in the UK Mild HCV trial and odds ratios for SVR with PEG 2b and IFN taken from a large multi-centre RCT. The incremental cost-effectiveness ratios (ICERs) for watchful waiting and early treatment with PEG are much greater than under the base case. The ICER for early treatment with PEG 2a compared with IFN is £23,252. This contrasts with a value of approximately £2000 for the base case with the low SVR for IFN.

The second scenario used a similar approach, but increased the difference between the SVR for PEG and IFN, based on outcomes for patients receiving higher doses of RBV. The ICERs were lower than for the previous analysis but were still greater than for the base case.

Changing the discount rates (from 6 to 3.5%) has a greater effect on the watchful waiting strategy than on early treatment. This has the effect of increasing the impact of costs borne in the future. Increasing the disease progression rates increases the cost-effectiveness of all strategies. Varying the health state utilities used in the model has a different impact between the early and delayed treatment strategies. There is little impact on the ICERs for the delayed treatment strategies, but an increase for the early treatment strategies.

The probabilistic analysis generated cost and QALY estimates for each intervention that were similar to those for the base case analysis. Early treatment with PEG appears to be the optimal intervention over a wide range of values for willingness to pay (which reflects the difference in SVR with PEG 2a against IFN in the data used in the evaluation), although there is a non-negligible probability that early treatment with IFN may be optimal. Results are similar for PEG 2b.

Conclusions

The results of this systematic review and economic evaluation show that patients with histologically mild HCV can be successfully treated with both PEG and IFN. Early treatment and watchful waiting strategies are associated with acceptable cost per QALY estimates.

Recommendations for future research

Research and development need to be directed towards newer, potentially more effective interventions, particularly those that improve treatment response in patients with genotype 1, with minimal adverse effects.

Further research is required into the natural history of HCV to estimate better the rate of liver disease progression, and also into the effectiveness of non-invasive biochemical markers of liver disease, as an alternative to liver biopsy.

Chapter 1

Aim of the review

The aim of this systematic review and economic evaluation is to assess the clinical effectiveness and cost-effectiveness of antiviral treatment in patients with mild hepatitis C virus (HCV) infection. Current practice is to treat patients only when their infection enters the moderate to severe stage. The assessment will therefore compare early treatment, when liver histology shows mild changes, with later treatment (moderate to severe liver disease). Treatment includes currently licensed drugs for HCV including pegylated and non-pegylated interferon alfa 2a and 2b (PEG and IFN), in combination with ribavirin (RBV). Outcomes include sustained viral, biochemical and histological response rates, health-related quality of life (HRQoL), adverse events, survival and costs per quality-adjusted life-year (QALY).

Chapter 2
Background

Description of underlying health problem

This section sets the context for this assessment report by describing the key features of HCV infection, its incidence and prevalence, the rate at which it progresses and a discussion of the use of biopsy and its alternatives to assess severity. It concludes by describing current practice in the management of HCV infection and outlining the proposed strategies for patients with mild HCV to be assessed in this report.

Background

Hepatitis C, first described in 1989, is a slowly advancing, insidious disease arising from transmission of the blood-borne HCV. The symptoms vary according to the severity of infection, with worsening liver damage a feature of disease progression. Acute infection is cleared by around 20% of patients, with the remainder developing chronic HCV. In the early stages of chronic infection, symptoms are generally mild although there may be a reduction in quality of life (e.g. tiredness, malaise, cognitive impairment). As the disease progresses, liver injury gradually occurs, in terms of tissue scarring (fibrosis) and inflammation, although this may not be noticed by the individual. Around 30% of people will become cirrhotic within 20 years. In worst cases, cirrhosis may progress to decompensated liver disease, where liver function can no longer be sustained because of fibrosis and inflammation. Decompensation is characterised by ascites, variceal bleeding and hepatic encephalopathy. Such patients will require liver transplant to survive, although the transplanted liver is highly likely to become infected and they will require prophylaxis and continued antiviral treatment. A small proportion of people (1–4%) will develop hepatocellular carcinoma. Factors associated with accelerated disease progression include male gender, older age at infection and excessive alcohol use [see the section 'Disease progression' (p. 9) for further detail on progression rates and associated factors].

The most common source of transmission in the UK is unsafe drug use, which accounts for around 90% cases. Many of these infections can be attributed to current or recent injecting drug use. However, some people may have become infected as a result of transient, experimental, phases of drug use in their earlier lives. The latter in particular may be under-reported due to poor recall (particularly if injecting took place several decades ago) and reporting bias (i.e. not wishing to disclose prior drug use due to social stigma). Some people, particularly immigrants, may have been infected abroad due to re-use of syringes and needles for therapeutic injections by medical personnel (e.g. Romania, where 4.5% are chronically infected with HCV). The World Health Organization (WHO)-supported Safe Injection Global Network (SIGN) estimates that each year re-use of dirty injection equipment causes an estimated 2.3–4.7 million infections with HCV.

The second main source of infection is contamination via infected blood products in patients with haemophilia prior to the introduction of blood screening in 1991 (although clotting factor concentrates were considered safe from 1985 when, with some exceptions in Scotland, viral inactivation began). Other, less common, sources of infection in UK include mother to baby transmission, occupational exposure (e.g. via needle stick injury), tattooing and body piercing.[1] The risk of sexual transmission is thought to be low,[2] although there is increasing evidence that existing HIV infection facilitates HCV transmission.[3] Prison populations are considered at particular risk for blood-borne infections such as HCV [and also HIV and hepatitis B virus (HBV)] due to sharing of contaminated needles for drug use, body piercing and tattooing. It is estimated that 60% of injecting drug users pass through the prison system at some point (DH Action plan).

There are six major genotypes and several subtypes of HCV, the prevalence of which varies geographically. Genotype 1a is common in North and South America and Australia, whereas genotype 1b is mostly found in Europe and Asia. Genotype 2a is common in Japan and China, genotype 2b is prevalent in the US and Northern Europe, genotype 3a is most common in Australia and South Asia and genotype 4 is commonly found in Egypt and central Africa. In England and Wales, the most prevalent genotypes are 3a (37%),

1a (32%) and 1b (15%). Type 3 is most common in injecting drug users[1,4] and type 1 in patients with haemophilia, infected via contaminated blood products.[1] As will be reported in the section 'Assessment of effectiveness' (p. 23), genotype is a key predictor of the effectiveness of antiviral treatment. Patients with genotypes 1, 4 and 5 tend to respond less well than patients with genotypes 2 and 3.

Defining mild hepatitis C

The severity of HCV has traditionally been determined by the classification of liver biopsy samples. However, there is some debate about the appropriateness of biopsy in some groups of patients. There has also been discussion about the reliability of biopsy classification systems. The following sections discuss these issues and attempt to provide some clarity about how mild HCV can be defined.

Use of biopsy

Liver biopsy is commonly performed to ascertain the severity of HCV and to enable the clinician and the patient to agree the best course of action. The Royal College of Physicians and the British Society of Gastroenterology in their clinical guidelines[5] state that the decision to offer treatment should be influenced by histological findings. They recommend that treatment can be reasonably withheld in patients with mild disease on liver biopsy but that these patients should be reviewed every 6 months, with repeat liver biopsy every 2–3 years or if there is a significant change in liver function tests (i.e. 2–3 times normal levels). If the biopsy shows evidence of progressive liver disease, treatment should then be considered. The guidelines also recommend that liver biopsy should be performed in all patients found to be viraemic, whether or not liver function tests are abnormal [e.g. alanine aminotransferase (ALT)].

More recently, a consensus conference at the Royal College of Physicians of Edinburgh in 2004 concluded that liver biopsy was no longer required in all patients. As one of the contributors commented, "Various British national guidelines continue to use liver biopsy as the gatekeeper to HCV therapy. However, with the advent of pegylated combination therapy, with cure rates of 80% for some genotypes, the rationale for this is difficult to justify given the morbidity and mortality of liver biopsies" (Ref. 6, p. 23).

Opposition to the use of biopsy stems from a number of arguments. First, biopsy can be a painful procedure, causing a great deal of discomfort to the patient. It is suggested that this might act as a barrier for patients coming forward for investigation and treatment, and that it contributes towards the relatively small number of patients treated in the UK.[7,8] Wider availability and acceptance of non-invasive liver tests might encourage more people to undergo assessment, and increase the current low uptake of treatment [see the section 'Antiviral treatment' (p. 13)].

Second, biopsy carries the risk of complications such as hepatic bleeding. This is particularly an issue for haemophiliacs. The Haemophilia Society reports that the majority of patients prefer not to undergo biopsy because of the risks of postoperative bleeding and the 2–3-day inpatient stay for administration of clotting factor.[9] In a minority of cases it is also associated with mortality (reported to be 0.03%).

Third, a biopsy may not be necessary in subgroups of patients most likely to attain a sustained viral response to antiviral treatment. In the pivotal trials of PEG and RBV in patients with moderate to severe HCV in the previous assessment report,[10,11] sustained virological responses (SVRs) were in excess of 80% in patients with genotypes 2 and 3 (the genotypes which tend to correlate most strongly with treatment response). Consensus is growing that these patients would automatically be eligible for treatment and consequently a biopsy would no longer be necessary to determine their treatment.[12] In 2003, a licence variation for PEG 2a was issued in Europe with the removal of the words 'histologically proven' hepatitis C from the indication.

Fourth, histopathological analysis of biopsy samples can be subject to poor inter-observer reliability, although this may be an idiosyncrasy of biopsy classification systems, rather than the biopsy itself [see the section 'Biopsy classification systems' (p. 5)]. Some histopathologists suggest that it is misleading to apply numerical scores to subjective interpretations of liver damage.

Fifth, the usefulness of a biopsy is influenced by sampling variation and the size of the biopsy sample itself. Smaller samples are likely to underestimate the severity of disease[13] and it is suggested that samples obtained in practice tend to be smaller than recommended (a length of at least 25 mm is proposed in one study[14]). Some biopsies yield intermediate results between mild and moderate to severe disease, in which case additional clinical factors may need to be considered in the management of a patient.

Finally, biopsy may become less important if antiviral treatment in patients with mild HCV is as effective as it is in patients with moderate to severe disease. It would no longer be necessary to gauge disease severity in order to decide when to treat. Rather, the majority of infected patients would be candidates for therapy.

Nevertheless, some defend the use of biopsy, suggesting that it can provide valuable clinical information on a range of issues, including:

- The most appropriate timing of therapy. The extent of disease progression (e.g. fibrosis) will guide decisions as to whether antiviral treatment should be commenced immediately or whether a period of watchful waiting is necessary. This will enable patients to plan ahead with the knowledge that at some point they may have to undergo treatment, which may impact on their domestic circumstances and their ability to work.[15,16] This may apply particularly to those with genotypes other than 2 or 3. In those with genotype 2 or 3, treatment with existing combination therapy is very successful. Those with other genotypes such as 1, but who do not at present have moderate or severe liver damage, might prefer to wait for more effective combinations of drugs to come along.
- Expectations of the outcome of therapy. The degree of fibrosis has been shown to be an independent predictor of the response to antiviral treatment.[17,18] The lower the degree, the higher is the SVR.
- The presence or absence of steatosis (fatty liver). A recent UK study found this to be present in 50% of liver biopsies,[19] and a review of 22 recent studies reported prevalence of between 40 and 70%. Its significance in the advancement of HCV is underpinned by studies such as that of Fartoux and colleagues,[20] who found it to be an independent factor predictive of progression of fibrosis.
- Other potential confounding liver diseases such as steatohepatitis and haemochromatosis, or iron accumulation, which can impact on prognosis.[15]

Replacing liver biopsy requires validated and effective alternative methods to gauge the extent of HCV-related liver damage. Non-invasive biochemical tests are in development, although some clinicians may not yet be convinced of their advantage over biopsy, and the tests may not yet be readily available in the UK [see the section 'Non-invasive biochemical markers of disease severity' (p. 6)].

In summary, although there is growing consensus for the selective use of biopsy in subgroups of patients with HCV, liver biopsy continues to be favoured by some clinicians in the UK as a key aspect of the assessment process.

Biopsy classification systems

The severity of HCV infection is usually determined by classification of liver biopsy samples as being mild, moderate or severe. Two components of a biopsy sample are used to determine severity. The first is fibrosis, the level of scarring that has occurred in the liver. The extent of fibrosis is expressed as a 'stage' which determines the position of the patient on the continuum of disease progression between its initiation (no fibrosis), and its final stage (decompensated cirrhosis). The second is necro-inflammation of the liver. This is expressed in terms of the 'grade' of disease activity, which is the rate at which the disease stage is changing. The inflammatory activity increases and decreases as the disease flares and subsides, or may remain constant.

There are a number of commonly used systems for classifying liver biopsy samples. Some share common characteristics and are derived from the same systems. Desmet and colleagues[21] provide an overview of the many different scoring systems available. The three most commonly cited are the Knodell Histological Activity index (HAI) (1981), the Ishak revised HAI (1995) and the METAVIR system (see Appendix 1 for further details).

In 1981, Knodell and colleagues[22] published a system comprising four components. The first three (periportal and/or bridging necrosis, intralobular degeneration and portal inflammation) are used to classify the extent of necro-inflammation. The maximum score for these components combined is 18. The fourth component indicates the amount of scarring (fibrosis) in the liver and is scored from 0 (no fibrosis) to 4 (cirrhosis). The total score based on all four components is 22. The Knodell system was introduced at a time of increasing research activity into antiviral treatment for chronic active hepatitis. Consequently, there was a need for a validated scoring system to evaluate changes in liver histology in clinical trials. The Knodell system has been widely adopted worldwide and is considered to be seminal.[21]

In 1995, Ishak and colleagues[23] published a revised version of Knodell's HAI (Ishak himself being one of Knodell's collaborators), primarily for use as a research tool. The revision was in recognition of some of the drawbacks of the original system. The revised system comprised four separate components for necro-inflammation grading (peri-portal or peri-septal interface hepatitis; confluent necrosis; focal (spotty) lytic necrosis, apoptosis and focal inflammation; and portal inflammation). The maximum score for necro-inflammation is 18. The fifth component refers to fibrosis staging, which has a maximum score of 6 (indicating cirrhosis). The total modified HAI score is 24 and is therefore a more complex scoring method with a broader range of potential scores.

In 1996, the French METAVIR Cooperative Study Group published an algorithm for the grading of activity in chronic hepatitis C.[24] This system differs from the Knodell and Ishak HAI in that it was specifically designed for use in HCV. The aim was to devise a simple method of scoring necro-inflammation grade and fibrosis stage. The former is scored on a scale of 0 (no histological activity) to 3 (severe activity), whereas the latter is scored from 0 (no scarring) to 4 (cirrhosis or advanced scarring of the liver). The total score possible is 7. The METAVIR system is considered to be the most validated instrument currently available, and has been used in a large number of published and clinical trials of antiviral treatment and cohort studies of natural history.

[Confidential information on comparability of scoring systems removed].

Staging fibrosis

Although both fibrosis and necro-inflammation are markers of disease severity, fibrosis is considered to be the strongest marker of true disease severity.[16] Under the Ishak system, if a biopsy fibrosis stage is scored as 6/6 then the person is classified as having severe HCV, irrespective of the necro-inflammatory score. As mentioned earlier, there is better inter-observer agreement between fibrosis scoring (Knodell) than necro-inflammatory, lending further support to prioritising fibrosis scores.[21,25]

Given the evolutionary development of biopsy classification systems over the last 25 years and the fact that a number of different systems have been used in the clinical trial literature, the question of their comparability arises. For example, how does an Ishak fibrosis score of 1 compare with a METAVIR fibrosis score of 2? Kleiner[15] compares five commonly used staging systems for chronic hepatitis C (see *Table 1*). As clinical guidelines[5] suggest that mild HCV is defined by an Ishak fibrosis score of ≤2/6, it can be determined that an Ishak 2 is comparable with ≤2 on the Batts and Ludwig[47] system and ≤1 on the METAVIR, Scheuer[122] and Knodell systems. A prospective biopsy study conducted at St Mary's Hospital, London, confirms this, demonstrating a significant correlation between biopsies scored with both the Ishak and METAVIR systems ($r = 0.96$, $p < 0.00001$).[26]

Kleiner[15] distinguishes between three transitions of fibrosis progression (represented by the three rows in *Table 1*). The first is the expansion from the normal non-fibrotic state into the portal area. This is followed by the development of fibrosis that bridges between vascular structures. The final stage is characterised by the formation of more and more bridges accompanied by distortion of architecture due to hepatocellular regeneration and contraction of fibrotic scars. This is cirrhosis.

Kleiner's thresholds of disease severity concur with Dienstag,[16] who reports the consensus to be the presence of septal/bridging fibrosis as the traditional indication for antiviral therapy (i.e. Ishak fibrosis score ≥3, METAVIR fibrosis score ≥2). Patients below these thresholds can therefore be considered as having mild HCV by virtue of ineligibility for treatment.

Non-invasive biochemical markers of disease severity

The effectiveness of non-invasive tests which could give information on the extent of liver damage was considered in the previous systematic review.[11] Briefly, the evidence reviewed at that time was that:

- There are limitations with liver biopsy [for reasons outlined in the section 'Disease progression' (p. 9)] including the assertion that biopsy might not give a representative picture of liver pathology. For example, Poynard and colleagues[27] noted that only 14% of biopsies were of size ≥25 mm.
- Panels of tests gave the best results, but many of these were complex. Some simple panels were useful in reducing the proportion of patients who needed biopsy, by identifying those with severe fibrosis and who would therefore be eligible for treatment, and those with very mild disease who then would not.

- For patients around the 'treat/do not treat' margin, the consensus was that the evidence for the effectiveness of non-invasive tests was not sufficient to replace histology.

However, the issue of the 'treat/do not treat' margin has changed. If antiviral treatment in patients with mild HCV proves to be effective, then many more patients will be eligible for treatment. How soon they start treatment may depend on a number of factors, including patient choice. The issue would then be when to treat not whether to treat.

A review by Poynard and colleagues[27] in 2004 concluded that biochemical markers could be used as the first-line assessment of liver fibrosis, although as in the past, the underlying rationale seems to have been about ruling out treatment of mild disease (the tests are judged on their ability to exclude significant fibrosis), which may no longer apply. However, the review is useful in the new era of deciding **when** to rule in treatment in those in whom it has been postponed. Poynard and colleagues concluded that liver biopsy still had a place as a second-line investigation in some patients.

New algorithms are being developed. Rosenberg and colleagues[28] examined a group of nine serum markers and developed an algorithm based on four factors (age, hyaluronic acid, tissue inhibitor of matrix metalloproteinase 1 and amino-terminal propeptide of type III collagen). This combination had very good sensitivity and specificity for significant fibrosis.

Summary

- There are debates about the appropriateness of liver biopsy in staging HCV and determining whether treatment is required. It is suggested that biopsy will be of less importance if antiviral treatment in patients with mild HCV is effective.
- A number of classification systems exist. There is some agreement about the threshold for defining mild fibrosis.
- Non-invasive tests for detecting fibrosis/cirrhosis are being developed. They may potentially be used as an alternative to biopsy.

Incidence and prevalence

It is believed that 100–170 million people worldwide are infected with HCV. The prevalence in the UK is uncertain, but is estimated to be between 0.1 and 1%.[29] In the UK there are an estimated 250,000–400,000 chronic infections.[30] Only around 38,000 of these are thought to be diagnosed, suggesting a substantial pool of undiagnosed infection. The longer these individuals remain undiagnosed, the further their liver disease will advance. In the coming decades, there may be a dramatic increase in the number of people presenting with HCV-related cirrhosis and decompensated liver disease, placing great burden on hepatology, gastroenterology and liver transplant services.

The Health Protection Agency (HPA) report that there were 60,000 laboratory diagnoses of HCV in the UK to the end of 2003.[31] *Table 2* shows laboratory reports between 1992 and 2003, stratified by sex. Reports have increased year on year over this period. The proportion of males infected is generally double that of females. The HPA also report data stratified by age group and region (data not shown; see www.hpa.org.uk). Reports are highest in the 25–44-year age groups and in the North West of England and London.

Data from the UK Trent HCV Study group show that the total number of anti-HCV positive patients recorded in the region (an assumed total population of 5.12 million) between 1991 and 1998 was 2546, representing a population-based prevalence of 0.05%.[1] This figure should be regarded as an underestimate, since it comes from population-based reporting of positive tests, and there will be other patients who are asymptomatic and who have not been tested. In common with the HPA figures, the study reported an annual increase in referred patients of 23.4% between 1991 and 1997.

The Department of Health (DoH) and the HPA have set up an HCV surveillance register to inform the natural history of HCV infection in the UK.[32] The register contains anonymised data for patients who have acquired their HCV infection on a known date. The majority of these are transfusion recipients who were traced during the national HCV look-back programme.

It is difficult to estimate the proportion of infections which could be considered as being mild since this currently requires verification by a liver biopsy. The number of infections which have been identified and verified histologically is likely to be relatively low. As patients with mild HCV are unlikely to experience hepatic symptoms, they are probably not aware of their infection and few will present to health services. Perceptions of liver biopsy as being a painful and potentially risky

TABLE 1 *A comparison of commonly used staging systems for chronic hepatitis C*

Knodell et *al.*, 1981[22]	**Scheuer, 1991**	**METAVIR, 1994[25]**	**Batts and Ludwig, 1995**	**Ishak et *al.*, 1995[23]**
0. No fibrosis 1. Fibrous portal expansion	0. None 1. Enlarged, fibrotic portal tracts	0. No fibrosis 1. Stellate enlargement of portal tracts without septae formation	0. No fibrosis 1. Portal fibrosis 2. Peri-portal fibrosis	0. No fibrosis 1. Fibrous expansion of some portal areas, with or without short fibrous septa 2. Fibrous expansion of most portal areas, with or without short fibrous septa
3. Bridging fibrosis (portal or portal–central linkage)	2. Peri-portal or portal–portal septa but intact architecture 3. Fibrosis with architectural distortion but no obvious cirrhosis	2. Enlargement of portal tracts with rare septae formation 3. Numerous septae without cirrhosis	3. Septal fibrosis	3. Fibrous expansion of most portal areas with occasional portal to portal (P–P) bridging 4. Fibrous expansion of portal areas with marked bridging [portal to portal (P–P) as well as portal to central (P–C)]
4. Cirrhosis	4. Probable or definite cirrhosis	4. Cirrhosis	4. Cirrhosis	5. Marked bridging (P–P and/or P–C) with occasional nodules (incomplete cirrhosis) 6. Cirrhosis, probable or definite

Taken from Kleiner.[15] Reprinted by permission.

TABLE 2 *Laboratory reports England and Wales, by sex, 1992–2003*

	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Male	160	297	570	1191	1784	2184	3011	3772	3406	3311	4035	4324
Female	74	129	249	414	688	793	1328	1744	1641	1487	1746	2036
Not known	7	9	20	41	55	61	140	209	186	159	117	139
Total	241	435	839	1646	2527	3038	4479	5725	5233	4957	5898	6499

Source: Health Protection Agency website. URL: www.hpa.org.uk. Accessed July 2005.

procedure may be an additional barrier to establishing the proportion of histologically mild patients.

In the Trent cohort study,[1] a biopsy was performed on 52.4% (588 of 1122) of the cohort, 397 of whom were scored using the Knodell classification system [see the section 'Biopsy classification systems' (p. 5) for more details of this and other systems]. Some 240 (60%) had a total Knodell score of <6 (out of 20), with 200 having a fibrosis stage score of 0, and 122 with a stage score of 1 (the threshold for mild disease in this system is ≤1/4). Only 33 (8%) had cirrhosis. Therefore, 322 (81%) of those biopsied could be classed as having histologically mild HCV. A 2004 publication from the Trent cohort study reported disease progression rates for a sample of 214 untreated patients assessed via paired biopsies (see the next section for further details of this study). A total of 183 patients (85%) were classified as having mild HCV based on an Ishak fibrosis score of 0–1 on the index biopsy. This is a relatively high proportion, although it should be noted that it is based on a cohort of patients presenting to various health services and who were not eligible for, or who did not wish to receive, treatment. They are therefore not necessarily representative of the undiagnosed population of people infected. In contrast, Booth and colleagues estimated in 2001 that only 25% of all patients presenting to health services have mild HCV.[5]

An analysis of a cohort of 845 patients presenting to the Viral Hepatitis Service in Newcastle upon Tyne found that 44% had histologically mild HCV (Ishak fibrosis score 0, 1).[33]

Disease progression

As mentioned earlier, people with moderate to severe HCV are at risk of progression to more advanced liver disease, including compensated and decompensated cirrhosis, and, in a small proportion, hepatocellular carcinoma. However, there has been uncertainty about whether people with milder HCV follow a similar course or whether their disease remains static.

The risk or rate of histological progression, and the associated risk factors, have been reported in observational studies of two forms:

1. Studies in which people underwent two (or more) biopsies, where the rate of progression was estimated from the change in fibrosis stages in the interval between samples.
2. Those in which the people underwent one liver biopsy, and the rate of progression was estimated from the interval between estimated exposure to the virus and the biopsy.

Either study design can estimate the risk of progression for underlying factors, but the paired biopsy sample method provides a stronger indication of the relationship between stage of fibrosis and subsequent disease progression. Studies commonly combine the two methods, reporting the paired biopsy sample group as a subset of the single-sample group.

Paired biopsy studies

Ryder and colleagues (Trent HCV Study Group),[34] Collier and colleagues,[35] and Wright and colleagues[26] have all recently published studies in which patients underwent two biopsies.

In Ryder and colleagues' study,[34] 214 untreated patients in the Trent region of the UK were prospectively examined, of whom 183 (85%) had mild fibrosis (Ishak F0 or F1). The median inter-biopsy interval was 2.5 years. During this time, 122 (57%) of patients experienced no change in fibrosis, 22 (10%) improved by one or more stages and 70 (33%) progressed at least one stage in fibrosis. Twenty-three (11%) progressed by at least two stages. On restricting the sample to only those with histologically mild disease, the proportions are slightly lower, with 25% progressing at least one fibrosis stage and 9% progressing by at least two (Ryder S, Trent-HCV study Group: personal

communication, 2005). The overall rate of progression was 0.17 Ishak stages per year, based on the assumption of linearity in progression. The authors conclude that histologically mild HCV is progressive. The overall rate of progression was low, but was accelerated in older patients and those with any fibrosis on their index biopsy.

Collier and colleagues[35] reported a prospective study based on a cohort of patients in Cambridge; 612 patients had undergone a biopsy, of whom they present data for 105 paired samples, separated by an average of 41 months. At index biopsy, most patients (80%) had moderate to severe disease (stage F2 or worse. The classification system is not reported, but fibrosis was scored between 0 and 5). It appears, therefore, that the proportion of patients in this study with histologically mild HCV is relatively low. Fibrosis stage remained the same in the majority of the sample. Improvement by one or more stages was experienced by 37 (35%) patients and worsening by one or more stage was seen in 23 (22%). Progression rates are given for the 20% or so of patients with initially mild fibrosis. Only a small proportion of these progressed. The calculated rate of progression for all patients in the sample was 0.15 stages per year. In summary, this study seems to suggest that disease progression is generally uncommon in the short term. The proportion of patients with initially mild disease is too low to be able to provide definitive estimations of progression in this subgroup.

In Wright and colleagues' study,[26] a cohort of 1606 patients at St Mary's Hospital, London with at least one biopsy are reported. The mean Ishak fibrosis score was 2.72 [standard deviation (SD) 1.7] and the median was 2 (0–6). The rate of fibrosis progression was non-normal with a marked right skew. The mean time to cirrhosis was 15 years, with a median of 35 years. A subset of 137 patients who had more than one biopsy is reported (after a mean of 33 months). The majority had mild disease on index biopsy. Fibrosis progression is presented only as a rate rather than a proportion, and also suggests an average rate of 0.15 stages of fibrosis per year. Based on the subgroup results, it was suggested that HCV is a slowly progressive disease, although this might be an artefact of the relatively short inter-biopsy interval. Wider intervals are recommended.

These studies are limited in their ability to compare mild with moderate to severe disease for a number of reasons:

- The interval between biopsies is only about half of the estimated time to progress one stage.
- The measure is an interval scale, not continuous, and may not be sensitive enough to detect small changes. Histochemical refinements have been unreliable.
- They use data from existing clinic cohorts and these do not include sufficient patients in each fibrosis category, and are therefore underpowered.
- The effect of unknown confounders is uncertain, but may be important.

It is difficult to make comparisons between these studies given the differences in methodology and case mix. However, rates of disease progression appear similar between mild and moderate to severe HCV.

All three studies report multivariate regression analyses to examine risk factors for disease progression. Findings are mixed:

- There is an association between baseline stage of fibrosis and probability of progression, with more severe disease progressing more rapidly.[34,35]
- Age at biopsy is important. Older people will progress more rapidly, suggesting non-linearity in progression.[34]
- Age at infection was significant in one study[26] but not in another.[34]
- Men may[26] or may not[34,35] progress more rapidly than women.
- Excessive current alcohol consumption was not linked with progression in two studies,[26,34] but was in another.[35]
- Genotype was not associated with progression in one study,[34] whereas in another genotype non-1 was.[26]
- Steatosis (fatty liver) was linked to progression in one study[35] but not in another.[34]

The interpretation of these findings is limited by the study design. For example, the lack of an association between progress and alcohol in Ryder and colleagues' study[34] may be due to the small numbers of heavy drinkers in their sample.

Single-sample studies

In this type of study, the researchers examined data for patients who have had only one liver biopsy. They estimate the duration of infection retrospectively from such data as the person can remember, or sometimes from the date of a specific high-risk event such as blood transfusion.

This may be unreliable due to the uncertainty of the source of infection and recall errors. It also assumes linearity in progression.

Poynard and colleagues 2001[36,37] report single biopsy sample studies. The 2001 publication[36] reports a total of 2313 patients with HCV, 62% of whom were histologically mild (METAVIR F0–F1). Fibrosis progression rates are reported for each individual METAVIR stage. For all stages there were four periods of linear progression: very slow (first 10 years), slow (following 15 years), intermediate (the following 10 years) and fast progression for the last 5 years. Three independent factors were associated with a faster progression rate: age at infection, alcohol consumption (50 g or more per day), and male gender ($p < 0.001$). They conclude that fibrosis progression is mostly regular from stage to stage, with progressive accelerations. Progression accelerates at 50 years of age, whatever the duration of infection.

The 2003 publication[37] reports a retrospective analysis of 4852 patients with chronic liver disease of a variety of causes (e.g. HCV infection, HBV infection, primary biliary cirrhosis). The aim was to compare fibrosis progression rates between the different diseases. About 55% of the sample were histologically mild at baseline (METAVIR F0–F1). The ages at which the probability of cirrhosis was 50% were 52 years (HIV–HCV co-infection), 61 years for alcoholic liver disease, 65 years for HBV infection, 72 years for HCV infection, 74 years for genetic haemochromatosis and 81 years for primary biliary cirrhosis. Disease progression is therefore fastest in patients co-infected with HIV–HCV.

Alberti and colleagues[38] review observational prospective studies, finding that in patients with histologically mild HCV progression tends to be faster in those with elevated ALT levels [see the section 'Service delivery' (p. 12)].

Disease progression – summary

Despite methodological limitations, these studies show that HCV is a progressive disease, although rates vary. Results from multivariate regression analysis on predictors of progression are mixed. Advanced age appears to play a role, as does fibrosis on baseline biopsy. Studies also suggest that patients with mild HCV **can** experience fibrosis progression over a relatively short period. This adds greater weight to considering antiviral treatment in this group.

Co-infection/co-morbidities

Given that the majority of HCV infections are due to injecting drug use, and that this is also a key source of transmission for other blood borne viruses, a proportion of patients will be co-infected with HIV and/or HBV.

Mohsen and colleagues[3] review the international literature on the epidemiology of HIV–HCV co-infected patients. They included 12 HCV sero-prevalence studies carried out in HIV-1-infected people in Europe and the USA. HCV prevalence ranged from 7 to 57%, largely influenced by risk factors in the study populations. Prevalence was highest in people with a history of injecting drug use (>80%). In each of the two haemophiliac studies, prevalence of HCV was 98%.

Evidence also suggests an increased rate of liver disease progression in HCV–HIV co-infected people. Graham and colleagues[39] conducted a meta-analysis of eight cohort studies and reported a pooled relative risk (RR) of 2.92 [95% confidence interval (CI) 1.70 to 5.01] for decompensated liver disease or histological cirrhosis. Mohsen and colleagues (2003)[40] report a study of 153 HCV infected and 55 HCV–HIV co-infected patients identified from two London hospitals. The estimated median fibrosis progression rate was 0.17 units/year in HIV–HCV co-infected and 0.13 in HCV mono-infected patients ($p = 0.01$). This equates to an estimated time from HCV infection to cirrhosis of 23 and 32 years, respectively. HIV positivity was also one of a number of factors independently related to fibrosis progression. A retrospective analysis of 4852 patients with chronic liver disease of a variety of causes by Poynard and colleagues[37] also confirms the role of co-infection in disease progression [see the section 'Disease progression' (p. 9) for further detail].

In terms of co-morbidities, a significant proportion of haemophiliacs in the UK are infected with HCV, due to contaminated blood products prior to the introduction of blood screening. It is estimated that 4865 haemophiliacs have been exposed to HCV, of whom around 1900 are living today with chronic hepatitis C (Morris J, Haemophilia Society: personal communication, 2005).

Health-related quality of life

As many people do not display obvious symptoms, it could be assumed that the burden of ill-health associated with HCV is minimal. However, non-specific symptoms including fatigue, irritability,

depression, nausea, headache, muscle ache, anorexia, abdominal discomfort and right upper quadrant pain have been reported.[41–43] Clinicians point out that patients' awareness that they carry a transmissible disease and the perceived risk of passing the disease to others can also significantly affect their quality of life. Although this psychological effect has not been specifically evaluated, it is a major motivator for patients to seek treatment. There is also some evidence to suggest cognitive impairment in patients with mild disease, a so-called 'brain fog'.[44,45]

The perception that chronic HCV infection has a marginal impact on HRQoL has been challenged in recent years. Studies evaluating HRQoL in HCV patients have used the Short Form with 36-items (SF-36) health survey. Derived from the Medical Outcomes Survey, the survey instrument comprises eight subscales, which evaluate the degree of impairment from a patient's ideal state of health.[46] The SF-36 is generally supplemented with several disease-specific scales to characterise particular problems experienced by patients (e.g. health distress, limitations caused by HCV infection).[41]

A study which examined the HRQoL of patients with HCV found that these patients scored significantly lower on all subscales of the SF-36 in comparison with population norms. The disease that was analogous to the HRQoL of the HCV group was type 2 diabetes, although chronic HCV patients scored significantly lower than diabetes patients on the vitality, social functioning and bodily pain SF-36 subscales.[48] However, a different conclusion was reached by a study conducted in Egypt.[49] HRQoL data were collected from 1286 people living in a remote village unaware of their serological status, using the SF-12 and a visual analogue scale (VAS). The prevalence of HCV infection was 146 (11.4%). There was no reduction in HRQoL for those with HCV compared with those without. The authors suggest that this might be due to a general lower morbidity rate among people with HCV in rural Egypt and a higher morbidity rate among those not infected (e.g. due to the relatively poor standard of living in rural areas). There are significant differences in the social, economic and demographic characteristics of the sample from those of studies conducted in Western countries, which may explain the findings.

One study found that HRQoL is impaired irrespective of the degree of liver inflammation or the mode of acquisition, suggesting that chronic infection with HCV in itself gives rise to symptoms that reduce the quality of life.[50] However, economic evaluations of antiviral treatment have employed higher baseline utility scores for people with mild HCV than for those with moderate HCV [see the section 'Supporting information on quality of life associated with chronic hepatitis C' (p. 61)]. This suggests that patients with mild HCV infection experience less morbidity than those with moderate disease (but who have not yet developed cirrhosis). For mild HCV patients, utility estimates varied from 0.77 to 0.98 (with 0 = death and 1 = perfect health). For moderate disease, the range was 0.66–0.92. These scores tend to be based on estimates given by clinicians, rather than patients themselves. Nonetheless, despite the disparity between these studies, mild HCV infection does not necessarily mean absence of morbidity.

HRQoL becomes further impaired during antiviral treatment, primarily due to the adverse effects associated with drugs, such as interferon. However, scores tend to return to baseline levels upon completion of treatment. An SVR is also associated with improvements in quality of life (although it is suggested that HRQoL scores of sustained responders remain slightly lower than population controls[51]). Increases in HRQoL due to successful treatment have been suggested to equate to meaningful improvements in the performance of daily activities and lower rates of tiredness and concern regarding hepatitis infection.[52] Hence, although the usual purpose of treatment is to prevent progression to more serious liver disease, in some patients it is worthwhile in terms of symptom relief and quality of life alone.

Current service provision

Service delivery

Patients with HCV are generally managed in specialist hepatology centres. Patients may also be managed in other specialisms by gastroenterologists and specialists in infectious diseases. Specialist hepatology nurses are also involved, particularly in the administration of antiviral treatment.

The National Plan for Liver Services in the UK provides an overview of the organisation of hepatology services in the NHS.[53] There are three categories of hospitals providing hepatology services:

- district general and university-associated hospitals that have a gastroenterologist with a primary interest in liver disease

- teaching hospitals with a major interest in liver disease that do not undertake liver transplantation
- liver transplant centres (n = 7).

The plan estimates that there are around 10–15 hospitals that would qualify as a hepatology centre and propose a set of criteria for qualification.

Managed Clinical Networks have recently been established which bring together commissioners (Primary Care Trusts), service providers, voluntary agencies, local authorities and service users to plan and deliver high-quality services, including prevention, screening, diagnosis, treatment and supportive care. It is envisaged that the number of networks will increase over the next few years and that one of their functions will be to increase capacity for delivering antiviral treatment.

Antiviral treatment

The aim of drug treatment is to clear the virus from the body, and success is usually taken to be a sustained drop in serum HCV RNA to undetectable levels. An SVR is generally considered to indicate permanent resolution of infection, and is associated with favourable changes in liver histology and reductions in liver enzymes such as ALT.

Currently, antiviral treatment is recommended only in patients with moderate to severe HCV. In 2000, NICE issued guidance to the health service in England and Wales recommending the use of interferon alfa in combination with RBV (or interferon monotherapy if RBV is contraindicated) in patients with moderate to severe HCV (Guidance Number 14). This was based on the assessment of the clinical and cost-effectiveness of interferon alfa and RBV.[54] In 2003, NICE updated their guidance to incorporate the newer pegylated form of interferon alfa, again, based on the updated assessment report[10,11] (Guidance Number 75). Briefly, the guidance recommends:

- PEG and RBV for people with histologically proven moderate to severe HCV, irrespective of whether previously treated, or treatment naïve. PEG monotherapy should be given where RBV is contraindicated.
- People with genotype 2 and/or 3 should be treated for 24 weeks.
- For people infected with HCV of genotype 1, 4, 5 or 6, initial treatment should be for 12 weeks. Only people showing, at 12 weeks, a reduction in viral load to less than 1% of its level at the start of treatment (at least a 2-log reduction) should continue treatment until 48 weeks. For people in whom viral load at 12 weeks exceeds 1% of its level at the start of treatment, treatment should be discontinued.
- PEG and RBV treatment is not indicated in people previously treated with, and not responding to, this combination, in people following liver transplant or for people under 18 years old.

The licensed indications for PEG and IFN alfa 2a and 2b, are provided in Appendix 2.

In 2003, the British Society of Gastroenterology (BSG) updated their 2001 clinical guidelines[5] on hepatitis C to take PEG into account.[55] Their revised guidelines were in line with NICE's 2003 guidance. The Scottish Medicines Consortium have also recommended PEGs for use in Scotland. Clinical guidelines are also available for subgroups of infected patients, such as those with haemophilia.[56]

Despite policy support for antiviral treatment, it is thought that only a relatively small proportion (5–10%) of infected patients actually receive therapy. Of the estimated 200,000–400,000 chronic infections in the UK, less than 40,000 are thought to be diagnosed (although it is estimated that less than 1% of infected haemophiliacs remain undiagnosed). It is not clear how many of the diagnosed pool will have mild HCV. As mentioned earlier, estimates may be from 25 to 85%. Irving and colleagues[57] conducted a study in the Trent region of England to determine whether patients diagnosed as anti-HCV positive are appropriately referred to specialist care. Of 11,177 patients tested, 256 (2.4%) were newly diagnosed as anti-HCV positive. Of these, 125 (49%) were referred appropriately, of whom only 26 (10%) commenced treatment. A total of 131 patients were not referred, and in 54 cases there was no evidence that the patient received the test result. Referral rates were highest from primary care and lowest from prisons. Non-attendance for specialist assessment was highest among patients referred from specialist drug and alcohol services and lowest among those referred from primary care or from prison/police. Inappropriate management and patient choice/drop-out were cited as reasons for the relatively low proportion of people progressing through the stages of the care pathway leading to antiviral treatment.

Use of biopsy

As discussed above, liver biopsy has traditionally been the accepted method of gauging the severity

of HCV-related liver damage. However, there is growing support for basing treatment decisions on clinical and serological markers (e.g. genotype). The published BSG guidelines from 2001 support the use of biopsy in the absence of the effectiveness of non-invasive tests. American guidelines also favour the use of biopsy.[58,59] Similarly, NICE's 2003 guidance recommends the use of biopsy as part of the assessment process. Nevertheless, they note that people for whom liver biopsy poses a substantial risk (such as those with haemophilia) may be treated on clinical grounds without prior histological classification. In contrast, the Royal College of Physicians and British Association for the Study of the Liver, in their joint submission to NICE for the appraisal of mild HCV, suggest the decision to undergo biopsy should only be made by the patient following an informed discussion with their doctor.[7]

Current service delivery in the UK is known to be variable.[30] BSG guidelines suggest that for patients who have received treatment, a repeat biopsy is probably not indicated. However, untreated patients undergoing a period of watchful waiting (e.g. patients initially with mild fibrosis) would be candidates for repeat biopsy every 3–5 years to monitor disease progression. There does not appear to be much indication about the optimum frequency of repeat biopsy, although US guidelines suggest an interval of 4–5 years.[59] A UK serial biopsy study to determine fibrosis progression suggests that longer intervals are necessary.[26] The Haemophilia Society in their submission to NICE report that practice in their patients is variable.[9] Some patients are biopsied every 3 years, whereas in others biopsy is contraindicated.

Injecting drug users

For current injecting drug users, the BSG 2001 guidelines suggest that antiviral treatment is not appropriate, for various reasons (e.g. poor compliance, risk of re-infection). However, the guidelines suggest treatment should be made available to injecting drug users (IDUs) in drug rehabilitation programmes. This subgroup of patients was also considered by NICE's 2003 guidance. They note that re-infection and poor adherence in continuing IDUs may not be as common as previously thought, and should not necessarily be a barrier to treatment. US National Institutes of Health guidelines (2002) also adopt a more lenient position, stating that current IDU patients should be evaluated on a case-by-case basis.

A 2004 systematic review identified seven studies of antiviral treatment in IDU patients, three of which were controlled trials.[60] Treatment included interferon alfa either as monotherapy or in combination with RBV, but none yet have used pegylated interferon. The authors report that there is no evidence to support withholding treatment to IDUs in methadone substitution programmes. However, the evidence was not sufficient to recommend treating people who had not been substituted. These were more likely to drop out of treatment and continue injecting. They recommend further large controlled trials with PEG.

Current practice in England and Wales for this patient group is likely to be variable. Some centres may restrict treatment to patients who have ceased injecting. In other areas, such as inner London, special hepatology clinics are run for IDUs.

Patients with persistently normal ALT

Antiviral treatment is generally only indicated in patients with elevated ALT levels (although the licence for PEG has recently changed to include patients with persistently normal liver enzymes). The management of patients with persistently normal ALT (PNALT) has been discussed in the literature.[61] PNALT can be defined as the presence of three consecutive measurements within the normal range during a 6-month period, although an 18-month period has been proposed. The BSG guidelines recommend the use of a biopsy whether or not liver function tests are normal or elevated.

Around 30–50% of people with chronic HCV present with normal ALT levels, and 70–80% continue to show normal levels when retested over a 6–12-month period (characterised as having PNALT). Between 20 and 25% of these have significant fibrosis, based on METAVIR score of ≥2. A further 20–25% of patients with initially normal ALT may develop transient exacerbations ('flares'), which are associated with rapid fibrosis progression.[61] This is possibly more common with genotype 2.

Alberti and colleagues[38] reviews observational prospective studies and outcome modelling projections of disease progression in histologically mild HCV patients. Studies indicate that the risk of liver disease progression towards severe fibrosis/cirrhosis is minimal at 10–15 years in people with PNALT, around 5–10% in patients with elevated ALT and F0 (no fibrosis) on the initial biopsy, but >30–40% in people with elevated ALT and F1 (portal fibrosis) on the initial biopsy.

In a separate publication, Alberti [61] reviews the epidemiological and clinical effectiveness evidence for people with PNALT, noting the emerging consensus that individualised assessment and treatment strategies are needed based on genotype, age, patient motivation and preference. He proposes an individualised treatment algorithm:

- Younger people (aged <45–50 years) with genotype 2 or 3, who are highly motivated, should be treated with PEG and RBV for 24 weeks, without biopsy.
- Antiviral treatment should be determined on the basis of a liver biopsy in patients with PNALT who are older than 50–65 years or infected with genotypes 1 or 4 or who have some contraindication. If they have no or minimal fibrosis (i.e. F0–F1), they should be monitored every 6 months. If they have more advanced fibrosis (≥F2), they should receive PEG and RBV for 24 or 48 weeks, depending on genotype.
- Patients above the age of 60–65 years who have a major contraindication to antiviral therapy, or are infected with genotypes non-1 and have a long duration of infection, should not undergo biopsy or receive antiviral treatment. They should be monitored every 6 months and avoid alcohol.

Description of new intervention

The proposal is to extend anti-viral treatment to patients with mild HCV, to underpin the 2006 extension of NICE guidance on PEG in patients with moderate to severe HCV. Since antiviral treatment in patients with mild HCV has never been appraised before at a policy level, it is necessary to assess the clinical and cost-effectiveness of both the current standard treatment, PEG, and the previous standard, IFN. This was specified in both the scope for the appraisal issued by NICE and the published peer-reviewed research protocol (these can be downloaded from www.nice.org.uk).

BSG guidelines recommend that treatment can be withheld in patients with histologically mild HCV, but that they should be followed to see if there is evidence of progressive liver disease by use of repeat biopsies.[5] The reason for withholding antiviral treatment in patients with mild disease is because it is unclear, in the absence of treatment, how many would progress to advanced disease (and at what rate) and how many would remain in their current disease state. Furthermore, the adverse effects associated with antiviral treatment can be difficult for some patients to tolerate and, given the uncertainty around what would be prevented by treatment, a policy of 'watchful waiting' has been employed. However, it has recently been suggested that treatment may be beneficial if an improvement in HRQoL can be demonstrated. Studies have shown that patients with HCV exhibit low quality of life scores independent of disease severity.[44,50] Symptoms include fatigue, nausea, depression, headache and cognitive impairment (so-called 'brain fog'). If treatment can be demonstrated to improve quality of life, this would add weight to the decision to treat this patient group.

The case for treating patients with mild HCV is strengthened by epidemiological modelling, which found that age at infection is an independent factor in disease progression.[36] Fibrosis progression rates tended to be higher in patients infected at an older age. After 50 years of age the progression of fibrosis accelerates rapidly, irrespective of duration of infection. This suggests the need to identify and successfully treat patients as early in their infection as possible, particularly those with advancing age.

Extending treatment to patients with mild HCV raises a number of issues. First, given the fact that a large proportion of people are suspected to be unaware of their infection, efforts to identify and assess them will need to be stepped up. Second, if efforts to increase the number of eligible people are successful increased funds will need to be set aside to pay for treatment. Third, some patients with mild HCV may not perceive their infection to be serious enough for them to endure and comply with antiviral treatment. They may not be prepared to experience the adverse effects associated with interferon treatment, and may opt to wait until newer, more tolerable, treatments are available.

Although antiviral treatment is not currently recommended by NICE in patients with mild HCV, clinical colleagues report that in some areas such patients are receiving therapy, particularly those with genotypes 2 and 3. In one area, it was estimated that 10% of genotype 1 patients with mild disease were treated last year, whereas the proportion of genotype 2 and 3 patients treated was around 50–60%. It was also noted that some genotype 2 and 3 patients are requesting treatment without a liver biopsy and some consultants are proceeding to treat without recommending a biopsy.

The cost of 24 weeks of treatment with IFN + RBV is around £4000 and for 48 weeks it is £8100. PEG 2b costs around £6500 for 24 weeks and £13,100 for 48 weeks. Corresponding costs for PEG 2a are £5000 and £11,900.

Chapter 3
Methods

A systematic review and economic evaluation were conducted to assess the clinical and cost-effectiveness of antiviral treatment for mild HCV. The review was guided by the general principles for conducting a systematic review proposed by the NHS Centre for Reviews and Dissemination (CRD).[62] Peer-review comments were sought from a panel of experts, in addition to NICE. The review followed the methods outlined in the published peer-reviewed research protocol (this can be downloaded from www.nice.org.uk).

Search strategy

A sensitive search strategy was developed, tested and refined by an experienced information scientist. Separate searches were conducted to identify studies of clinical effectiveness, cost-effectiveness, quality of life, resource use/costs and epidemiology/natural history (see Appendices 3–6 for search strategies). Search filters were run where possible to locate randomised controlled trials (RCTs) and systematic reviews. The strategies were applied to the following electronic databases:

- Cochrane Systematic Reviews Database
- Cochrane Central Register of Controlled Trials
- NHS CRD (University of York) databases: DARE (Database of Abstracts of Reviews of Effects), Health Technology Assessment (HTA) database, NHS EED (Economic Evaluations Database)
- MEDLINE (Ovid)
- PreMEDLINE
- PubMed
- EMBASE (Ovid)
- EconLit
- National Research Register
- ISI Web of Science – Science Citation Index
- ISI Web of Knowledge Proceedings
- BIOSIS
- clinical trials.gov
- Current Controlled Trials.

Searches were designed to build on the searching employed in the previous assessment reports on (non-pegylated) interferon alfa in 2000,[54] and pegylated interferon alfa in 2004,[11] as follows:

- Searches for clinical effectiveness and cost-effectiveness studies of PEG were run from 2003 to July 2005 (our previous assessment report on PEG for HCV searched up to the end of 2002).
- Searches for clinical effectiveness and cost-effectiveness studies of IFN were run from 2000 to July 2005. The previous assessment report on IFN for hepatitis C searched up to the end of 1999/early 2000. To identify studies published prior to 2000, the original database was re-screened, looking specifically for RCTs which included patients with mild HCV.
- A search for general cost and cost-effectiveness studies in HCV (i.e. not limited to just interferon alfa) was run from 2000 to July 2005.
- Searches for HRQoL and epidemiological/natural history studies were run from 2003 to July 2005.

Bibliographies of retrieved papers were screened, where possible, for relevant studies. Manufacturer and sponsor submissions to the NICE were also searched for studies. All search results were downloaded into a Reference Manager database.

The following websites were also searched for completed or on-going studies and background material:

- British Association for the Study of the Liver (BASL)
- European Association for the Study of the Liver (EASL)
- American Association for Study of Liver Diseases
- British Society of Gastroenterology (BSG)
- Foundation for Liver Research
- British Liver Trust
- British Association for Sexual Health and HIV
- HIV and Hepatitis.com
- Food and Drug Administration
- Health Protection Agency
- Department of Health (England).

Inclusion and exclusion criteria

Each study was screened on the basis of title and/or abstract for inclusion by one reviewer. A random 10% sample of these was screened independently by a second reviewer. Publications for those marked as relevant were then ordered for

further screening. An inclusion worksheet was used (see Appendix 7). Further details on the criteria are set out below.

Interventions

Studies reporting the following interventions were included:

1. pegylated interferon
   (a) dual therapy (PEG 2a/PEG 2b and RBV).
   (b) monotherapy (for patients who are unable to tolerate RBV) (PEG 2a/PEG 2b)
2. non-pegylated interferon
   (a) dual therapy (IFN 2a/IFN 2b and RBV)
3. comparisons
   (a) best standard care, including either treatment without any form of interferon therapy (e.g. best supportive care) or (for pegylated interferon) treatment with non-pegylated interferon (i.e. IFN 2a/IFN 2b) where evidence allows.

Patients

With a few exceptions, it is not always apparent from the title or abstract of a clinical trial whether or not the patients included have mild, moderate or severe HCV. It is therefore necessary to examine the baseline characteristics of included patients (where reported) to assess the proportion who can be classed as having histologically mild liver disease.

As discussed in the section 'Use of biopsy' (p. 4), the result of a liver biopsy is generally the most accepted way of gauging disease severity. Clinical guidelines issued by The Royal College of Physicians/BSG provide the following definition of mild HCV:

> "Histological appearances are classified as mild if the fibrosis score (stage) is less than or equal to 2/6, and if the necroinflammatory score (grade) is less than or equal to 3/18 (Ishak). If the fibrosis score is 3–5/6 and/or the necroinflammatory score is greater than 3/18, the appearances are described as moderate. If the fibrosis score is 6/6, the biopsy is cirrhotic irrespective of necroinflammatory score."[5]

The scope for this appraisal, issued by NICE, adopts this definition but notes that other classification systems are in use (e.g. METAVIR, Knodell) [see the section 'Biopsy classification systems' (p. 5)]. In order to be as inclusive as possible, inclusion was not restricted to any particular classification system.

In setting the inclusion criteria there were a number of uncertainties. First, clinical hepatology experts consulted suggested that choosing a threshold, in terms of fibrosis scores, between mild and moderate HCV can be arbitrary. For example, whereas some might consider an Ishak fibrosis score of ≤1 as defining mild HCV, others might consider a slightly higher threshold of ≤2. However, advice from histopathologists and a published comparison of fibrosis scoring thresholds of widely used biopsy classification systems helped to provide some clarity around this issue [see section 'Staging fibrosis' (p. 6)].

Second, there was no guidance on the proportion of mild patients that should be present in a clinical trial to warrant inclusion in an assessment of clinical effectiveness.

Third, expert clinical opinion suggests that the degree of liver fibrosis, as opposed to the degree of necro-inflammation, is a stronger indication of disease severity.

Taking all of the above into account, the following criteria were used. For a trial to be classed as including patients with mild HCV, no less than 70% of enrolled patients had to be classed as mild on initial biopsy (however, a trial with less than 70% of mild patients may be considered for inclusion if outcomes are reported for the subgroup of patients with mild HCV in addition to moderate to severe HCV). *Table 3* reports the fibrosis thresholds employed.

Mean or median scores, if reported, should be lower than the threshold for each classification system.

Types of studies

Systematic reviews of RCTs and Phase II/III RCTs were included that compared the different drugs with placebo, each other or best supportive care in the review of clinical effectiveness. Also included were full economic evaluations of the specified interventions in patients with chronic mild HCV. For studies reporting HRQoL and epidemiology/natural history, a range of study designs were

TABLE 3 *Fibrosis thresholds*

Classification system	Fibrosis threshold
Knodell	≤ 1/4
Ishak	≤ 2/6
METAVIR	≤ 1/4
Scheuer	≤ 1/4
Batts and Ludwig, 1995	≤ 2/4

included (e.g. cohort studies, cross-sectional surveys). Studies published as abstracts or conference presentations were included in the primary analysis of clinical and cost-effectiveness.

Outcomes

The following outcome measures were included:

- virological response (12 weeks of treatment, end of treatment and end of follow-up)
- histological improvement (e.g. inflammation/fibrosis – on biopsy)
- biochemical response (e.g. liver function – ALT)
- adverse effects of treatment
- survival
- HRQoL.

Data extraction strategy

Data were extracted from the included clinical effectiveness studies using a standardised template. Data extraction was undertaken by one reviewer and checked by a second, with any disagreements resolved through discussion. Full data extraction forms of all the included studies can be found in Appendices 8–17.

Quality assessment strategy

The quality of included systematic reviews and RCTs was assessed using NHS CRD (University of York) criteria.[62] Quality criteria were applied by one reviewer and checked by a second, with any disagreements resolved through discussion.

Methods of analysis/synthesis

A narrative synthesis was undertaken with the main results of the included clinical effectiveness and cost-effectiveness studies described qualitatively and in tabular form. A meta-analysis was not possible due to heterogeneity in the interventions and comparators evaluated. Where data allowed, clinical and cost-effectiveness were assessed according to patient subgroups (e.g. by genotype, baseline viral load).

Chapter 4

Clinical effectiveness

Results

Quantity and quality of research available

Literature searching identified 2652 references to studies of the clinical effectiveness of treatments for HCV. These were screened for inclusion on title and abstract. A further 211 studies identified from searches conducted for the previous assessment report[54] on IFN were re-screened. The total number of records screened was therefore 2863. Of these, 2352 were excluded because they did not meet the inclusion criteria (e.g. they were observational studies and/or they evaluated a non-interferon alfa intervention).

Full reports (where available) of the remaining 511 were requested for further screening. Of these:

- 21 were included.
- 256 were excluded.
- 232 were unclear.
- 2 were unclassified.

Studies excluded on full report (n = 256) failed to meet one or more of the inclusion criteria of:

- including patients with histologically mild HCV
- reporting an RCT or systematic review
- evaluating PEG/IFN
- reporting a relevant outcome measure.

The 232 studies judged 'unclear' met the criteria for inclusion in that they were either an RCT or systematic review, evaluated PEG or IFN and reported relevant outcome measures. However, the proportion of patients with histologically mild HCV could not be determined for one or more of the following reasons:

- No baseline histology profile was reported.
- No baseline fibrosis score was reported.
- No report of which biopsy classification system was used or the classification system was unclear.
- Reports only the proportion of patients with bridging fibrosis or cirrhosis at baseline such that it was not possible to delineate the proportion of patients with fibrosis scores that indicate mild HCV. On some classification systems it cannot be assumed that anything less than bridging fibrosis/cirrhosis is mild HCV.

Without further detail, it was not possible to judge what proportion of the patients included in these trials could be classed as having mild HCV, in accordance with the criteria reported in the section 'Patients' (p. 18).

It was not possible to retrieve full reports for two unclassified studies.

- The section below and the section 'Assessment of effectiveness' (p. 23) present details of eight RCTs of antiviral combination therapy in patients with mild HCV.
- The section 'Monotherapy trials' (p. 42) presents brief details of two RCTs of monotherapy in mild HCV patients.
- The section 'Studies reporting subgroups of mild HCV patients' (p. 43) presents brief details of 11 studies of reporting the effectiveness of antiviral therapy in subgroups of patients with mild HCV and moderate to severe HCV.

Trials of antiviral treatment in mild HCV patients

Overview of the trials

Eight RCTs of antiviral treatment in mild HCV patients were identified and included.[63–70] Five of the studies evaluated IFN 2b,[63–65,67,70] and three evaluated PEG 2a.[66,68,69] The five interferon studies compared IFN 2b in combination with RBV with either no treatment[65] or IFN 2b monotherapy.[63,64,67,70] Three of these employed the standard 3 million international units (MU) dose of IFN, given three times per week,[64,65,70] and two used higher doses of 5 MU[63] or 6 MU,[67] again given three times per week.

The dose of PEG 2a was the same in all three studies (180 µg once weekly), but the comparative intervention arms differed. Zeuzem and colleagues[66] incorporated three arms, evaluating PEG 2a in combination with RBV for 24 weeks versus the same treatment for 48 weeks versus no treatment. Hadziyannis and colleagues[69] included four treatment arms of PEG 2a plus RBV, assessing a low (800 mg/day) versus high (1000–1200 mg/day) dose of RBV and treatment

duration (24 versus 48 weeks) in a factorial design. The third study, by Chung and colleagues,[68] was a direct comparison of PEG 2a with IFN 2a (6 MU followed by 3 MU three times per week) both in combination with RBV in ascending doses (600–1000 mg/day) in patients co-infected with HIV–HCV.

Treatment duration ranged from approximately 6 months to 1 year, with participants followed up for approximately 6 months in all the studies. In the Zeuzem trial,[66] participants in one treatment arm were followed up for 48 weeks post-treatment cessation.

The key characteristics of the RCTs are shown in *Table 4*. All but one study were multicentre trials. Five RCTs recruited patients from a number of centres within one country (Sweden,[64,70] Italy,[63] the USA[68] and the UK[65]) and one trial recruited patients from one hospital site in Taiwan.[67] The two larger PEG trials[66,69] were international RCTs with 70–99 participating centres across Australia, Europe, New Zealand, Taiwan and North and South America. One trial was sponsored by the UK Health Technology Assessment (HTA) programme,[65] one was funded by the US National Institutes of Health,[68] five were funded by the drug manufacturers[64,66,67,69,70] and one did not state the funding source but did receive RBV from the drug manufacturer.[63]

All the trials were based on middle-aged (mean age range 36–49 years) adult patients, with the proportion of male participants ranging from 40 to 82%. Patients were treatment naïve in all but one study,[67] which included patients who had relapsed after having previously responded to IFN treatment. The five IFN trials varied in size, ranging from 52 to 196 participants, of whom approximately half were genotype 1 in all five RCTs. One of the PEG trials[68] included 133 patients, whereas the other two PEG trials[66,69] were much larger, involving 491–1284 patients. Approximately two-thirds of participants had genotype 1 in all three PEG trials. In terms of ethnicity, the large majority (86–90%) of participants were white, as reported by three RCTs,[65,66,69] with one trial[68] consisting of approximately 50% white participants. The source of infection varied between studies. The proportion of patients infected by intravenous drug use ranged from 21 to 60% and those infected by blood transfusion ranged from 6 to 23%. Four different classification systems were used for reporting histological findings; three trials used the Ishak,[65,66,68] three used the Knodell,[64,67,69] one used the Scheuer[63] and one used the Batts and Ludwig[70] system.

In general, all eight RCTs used similar inclusion criteria, except in relation to ALT levels and, to a certain extent, fibrosis. Four studies specified that included patients had raised ALT levels for at least 6 months,[63,64,69,70] one specified that patients had persistently normal ALT levels[66] and two studies accepted either raised or normal ALT levels.[65,68] In terms of fibrosis stage, the trials by Wright and colleagues.[65] and Verbaan and colleagues.[64] stipulated that only patients with mild HCV were eligible for inclusion (Ishak fibrosis score ≤2, Knodell fibrosis stage ≤1, respectively). Although the other trials did not specify an upper limit for fibrosis in their criteria, they included all or largely mild patients. Patients with cirrhosis were eligible for inclusion in the trial by Chung and colleagues[68] provided that there was no evidence of hepatic decompensation. This trial also differed from the other trials in that patients were required to be HIV positive.

Exclusion criteria were similar in all included trials. All eight excluded participants who had various existing co-morbidities. Four trials reported excluding patients with 'concomitant significant medical illness'[63,67,69] or 'other serious systemic disease'.[66] Other conditions were specifically stated. All but one trial[68] excluded patients with HIV co-infection, five of which also excluded those with concurrent hepatitis B[63,64,67,68,70] and two with hepatitis A or B co-infection.[66,69] Liver disease of other aetiology excluded participants in five studies.[64–67,70] Patients with decompensated cirrhosis[63,64,66–70] or transition to cirrhosis on biopsy[66] were also generally excluded. Most trials excluded patients with evidence of current/recent high alcohol intake or intravenous drug use, and also psychiatric conditions. Most trials excluded participants with co-morbidities such as anaemia,[63,64,66–69] autoimmune diseases[63–65,67,69,70] and cardiac disease.[64–69] Three trials excluded patients with diabetes mellitus.[63,65,67] Four trials excluded patients who had had an organ transplant.[65–67,69] One trial excluded patients with PNALT levels,[64] whilst in contrast, another trial excluded patients with one or more elevated ALT levels (within the previous 18 months).[66]

Many of the trials stipulated certain laboratory readings in their exclusion criteria, most of which related to conditions which are consistent with decompensated liver cirrhosis. Six trials[63,64,66–69] excluded patients with thrombocytopenia,

requiring platelet counts ranging from less than 90,000 to less than 100,000 cells/mm^3. Five[64,66–69] excluded patients with neutropenia where neutrophil counts ranged from less than 1500 to less than 2000 cells/mm^3. Three[63,64,67] excluded patients with low white blood cell counts ranging from less than 3000 to less than 4000 cells/mm^3. Six[63,64,66–69] excluded patients with anaemia who had haemoglobin ranging from below 11.5 to 12 g/dl for women and below 13 g/dl for men. One trial[63] excluded patients with serum albumin less than 35 g/l, and two trials[66,69] excluded participants with serum creatinine levels over 1.5 times the upper limit of normal.

Other exclusion criteria included chronic pulmonary disease,[64,69] haemophilia,[65,67,70] renal disease,[67,68] malignancy,[64,69] retinal abnormalities,[67,69] active HIV-related opportunistic infection,[68] pregnancy/breast-feeding,[63,64,67,69,70] unwillingness to practise contraception,[65,67,69] and previous treatment with interferon or RBV.[63,70]

The primary outcome measure in the majority of RCTs was an SVR, defined as undetectable serum HCV-RNA at 6 months post-treatment cessation. Chung and colleagues,[68] who treated patients for 48 weeks, reported SVR as a secondary outcome measure, with the primary outcome measure being virological response at week 24 of treatment. End of treatment virological response, and also SVRs, were reported in all the RCTs with the exception of that of Zeuzem and colleagues,[66] which reported only SVR. Two trials[63,68] also reported 'early' virological response after the first 12 and 24 weeks of treatment, respectively. In terms of secondary outcomes, three trials reported normalisation of ALT values[63,67,70] and four trials[64,67,68,70] measured change in liver histology. The trial by Wright and colleagues[65] was the only one to include quality of life as a secondary outcome measure. In addition, all eight trials measured the effect of various baseline characteristics (e.g. genotype, age, viral load) on SVR and four trials reported the predictive value of early virological response.[63,65,67,68] All eight trials reported adverse events.

The methodological quality of reporting in the included studies was assessed using criteria set by the NHS CRD at the University of York[62] and is shown in *Table 5*. In general, the RCTs were of good quality, with the trial by Hadziyannis and colleagues[69] ranking highest in its reporting of methodological details. In seven trials, the groups appeared similar at baseline on important demographic, histological and prognostic characteristics, although in some cases supporting statistical comparisons were not presented. Only two trials[64,69] explicitly reported a randomisation procedure that ensured true random assignment to treatment groups; for five trials,[64–66,69,70] the use of a central randomisation procedure ensured adequate concealment of allocation.

Blinding of participants and outcome assessors helps to guard against systematic differences in assessment of outcomes for the different groups. Given the disparity in the treatment interventions (e.g. different drug regimes or duration), four of the trials were open label[63,65,66,68] and therefore the assessment of patient blinding was not applicable. In three trials of IFN 2b, there was patient blinding as to whether participants were receiving RBV or placebo in addition to IFN.[64,67,70] In the PEG 2a trial by Hadziyannis and colleagues,[69] investigators and patients were blinded to RBV dose and treatment duration (until week 24). This was the only trial to specifically mention blinding of outcome assessors, although three other trials[63,65,66] reported that assays were performed by a single laboratory. In five of the trials,[63,64,67,68,70] liver histology was assessed by the same pathologist who was unaware of the patients' assignment or treatment response.

All trials performed an intention-to-treat (ITT) data analysis for the primary outcome of SVR, analysing the results of all randomised patients,[63,67,68,70] or all patients who received at least one dose of study medication.[64–66,69] Only three trials[63,66,69] reported the primary outcome adequately by providing measures of variability (CIs). Conversely, only two trials[64,66] failed to report adequately details of withdrawals and losses to follow-up. Although all the trials conducted a power analysis, two trials[66,69] did not report the optimum sample size required.

Assessment of effectiveness

This section presents the results of the included RCTs in terms of primary and secondary outcomes: virological response and SVR, biochemical response (ALT), histological response (change in fibrosis) and HRQoL.

Virological response

Table 6 reports SVRs for two of the three PEG trials. In the trial by Zeuzem and colleagues,[66] treatment for 48 weeks with PEG 2a was significantly more effective than the same treatment for 24 weeks (SVR 52 vs 30%, $p < 0.001$), with an RR of 1.7 (95% CI 1.4 to 2.2). No patient in the untreated control group cleared

TABLE 4 *Key characteristics of included studies – participants and outcomes*

Study	Methods	Key inclusion/exclusion criteria	Other patient characteristics	Outcomes
Cheng *et al.*, 2002[67]	*Design:* single-centre, double-blind RCT *Number of centres:* 1 *Sponsor:* Schering-Plough and National Cheng-Kung University Hospital, Taiwan *Country:* Taiwan *Interventions:* IFN 2b + RBV vs IFN 2b + placebo for 24 weeks *Follow-up:* 24 weeks post-treatment *No. participants:* 52	*Inclusion criteria:* • Adult patients who had previously responded to IFN and subsequently relapsed • HCV RNA positive • Positive antibody to HCV antibody test • Using effective contraception	• Fibrosis system: Knodell • Mean fibrosis stage: 0.5 Group 1, 0.2 Group 2 • Liver biopsy taken: before and at end of treatment • Mean HCV RNA, ~7.5 MEq/ml • Average age: ~44 years • Gender: 79% male • Genotypes: 42% 1b, 6% 1a+2, 42% 2a + c, 4% 2b, 6% 2 (not subtyped) • Mode of infection: not reported • Ethnicity: not reported	*Primary outcomes:* • SVR *Secondary outcomes:* • Biochemical response (normalisation of ALT values) • Change in liver histology • Adverse events
Chung *et al.*, 2004[68]	*Design:* multicentre, open-label RCT *Number of centres:* 21 *Sponsor:* National Institutes of Health *Country:* USA *Interventions:* Peg IFN 2a + RBV vs IFN 2a + RBV for 48 weeks *Follow-up:* 24 weeks post-treatment *No. participants:* 133	*Inclusion criteria:* • Treatment-naïve adult patients • HCV RNA positive • HIV positive • Biopsy findings consistent with a diagnosis of chronic hepatitis C • Normal or elevated ALT levels • Cirrhosis acceptable provided that there was no evidence of hepatic decompensation	• Fibrosis system: Ishak • Median fibrosis stage: 2.0 Group 1, 2.0 Group 2 • Liver biopsy taken: ≤48 weeks before study entry • Mean HCV RNA, 6.2×10^6 IU/ml • Average age ~45 years • Gender: 82% male • Genotype 1: 78% • Mode of infection: not reported • Ethnicity: 48% white, 33% black, 14% Hispanic, 5% other	*Primary outcomes:* • Virological response at week 24 of treatment *Secondary outcomes:* • SVR • Histological response • Adverse events
Hadziyannis *et al.*, 2004[69]	*Design:* multicentre, double-blind RCT *Number of centres:* 99 *Sponsor:* Roche *Country:* USA *Interventions:* PEG 2a + RBV (low dose), 24 weeks PEG 2a + RBV (standard dose), 24 weeks PEG 2a + RBV (low dose), 48 weeks PEG 2a + RBV (standard dose), 48 weeks *Follow-up:* 24 weeks post-treatment *No. participants:* 1284	*Inclusion criteria:* • Treatment-naïve adult patients • HCV RNA positive • Biopsy findings consistent with a diagnosis of chronic hepatitis C • Raised ALT within previous 6 months • Compensated liver disease	• Fibrosis system: Knodell • Fibrosis stage 0, 1: 75% • Liver biopsy taken: ≤15 months before study entry • Mean HCV RNA: $\sim 5944 \times 10^3$ copies/ml: • Average age: ~42 years • Gender: 65% male • Genotypes: 58% 1, 42% non-1, 16% 2, 38% 3 • Mode of infection: 36% IDU, 18% transfusion, 33% unknown/other • Ethnicity: 89% white, 3% black, 7% Asian, 1% other	*Primary outcomes:* • SVR *Secondary outcomes:* • Adverse events

continued

TABLE 4 *Key characteristics of included studies – participants and outcomes (cont'd)*

Study	Methods	Key inclusion/exclusion criteria	Other patient characteristics	Outcomes
Mangia *et al.*, 2001[63]	*Design:* multicentre, open-label RCT *Number of centres:* 9 *Sponsor:* not stated *Country:* Italy *Interventions:* IFN 2b + RBV vs IFN 2b for 12 months *Follow-up:* 6 months post-treatment *No. participants:* 192	*Inclusion criteria:* • Treatment-naïve patients • HCV RNA positive • Histopathological evidence of chronic hepatitis (liver biopsy taken ≤6 months before enrolment) • Raised ALT for at least 6 months	• Fibrosis system: Scheuer • Fibrosis stage 0, 1: 77% • Liver biopsy taken: ≤6 months before enrolment • HCV RNA: ~6.4×10^6 equivalent genomes/ml • Average age ~47 years • Gender: 67% male • Genotypes: 47% 1b, 34% 2a, 14% 3, 5% other • Mode of infection: 21% IDU, 6% transfusion, 73% community acquired • Ethnicity: not reported	*Primary outcomes:* • SVR *Secondary outcomes:* • Biochemical response (normalisation of ALT values) • Adverse events
Reichard *et al.*, 1998[70]	*Design:* multicentre, double-blind RCT *Number of centres:* 5 *Sponsor:* Schering-Plough *Country:* Sweden *Interventions:* IFN 2b + RBV vs IFN 2b + placebo for 24 weeks *Follow-up:* 24 weeks post-treatment No. participants: 100	*Inclusion criteria:* • Adult patients (age >18 years or <70 years) • HCV RNA positive • Biopsy findings consistent with a diagnosis of chronic hepatitis C (biopsy taken in preceding 12 months) • Positive antibodies to HCV antibody test • Persistently raised aminotransferases for at least 6 months	• Fibrosis system: Batts and Ludwig • Mean fibrosis stage: ~1.5 • Liver biopsy taken: ≤12 months before study entry and at week 24 • Geometric mean HCV RNA: ~3.6×10^6 Eq/ml • Average age: ~39 years • Gender: 62% male • Genotypes: 17% 1a, 19% 1b, 3% 1 (not subtyped), 5% 1a + b, 1% 2a, 17% 2b, 1% 2a + b, 33% 3a, 2% 4 (not subtyped), 1% 4c + d, 1% 5a • Mode of infection: 51% IDU, 16% transfusion, 33% unknown • Ethnicity: not reported	*Primary outcomes:* • SVR *Secondary outcomes:* • Biochemical response • Change in liver histology • Adverse events

continued

TABLE 4 *Key characteristics of included studies – participants and outcomes (cont'd)*

Study	Methods	Key inclusion/exclusion criteria	Other patient characteristics	Outcomes
Verbaan *et al.*, 2002[64]	*Design:* multicentre, double blind RCT Number of centres: 15 *Sponsor:* Schering-Plough *Country:* Sweden *Interventions:* IFN 2b + RBV vs IFN 2b + placebo for 52 weeks *Follow-up:* 26 weeks post-treatment *No. participants:* 116	*Inclusion criteria:* • Treatment-naïve patients (age 18–60 years) with histologically mild chronic HCV infection • Knodell fibrosis stage ≤1, Knodell activity score ≥1 and ≤6 • HCV RNA positive (liver biopsy taken within previous 12 months) • Raised ALT for at least 6 months	• Fibrosis system: Knodell • Mean fibrosis stage: 0.4 Group 1, 0.3 Group 2 • Liver biopsy taken: not reported • Viral load, mean HCV RNA bDNA version 3: 2.34×10^6 copies/ml Group 1, 9.16×10^5 copies/ml Group 2 • Average age: ~37 years • Gender: 59% male • Genotypes: 35% 1a, 14% 1b, 16% 2b, 32% 3a, <1% 4, 2% missing/unknown • Mode of infection: 60% IDU, 9% transfusion, 7% other, 24% unknown • Ethnicity: not reported	*Primary outcomes:* • SVR *Secondary outcomes:* • Change in liver histology • Adverse effects
Wright *et al.*, 2005[65]	*Design:* multicentre, open-label RCT Number of centres: 13 *Sponsor:* HTA programme *Country:* UK *Interventions:* IFN 2b + RBV vs no treatment for 48 weeks *Follow-up:* 24 weeks post-treatment *No. participants:* 196	*Inclusion criteria:* • Treatment-naïve adult patients with mild chronic hepatitis C (Ishak necro-inflammatory score ≤3, fibrosis score ≤2) • HCV RNA positive • Normal or raised ALT	• Fibrosis system: Ishak • Mean fibrosis stage: 1.01 for treatment group, 1.18 for control group. • Liver biopsy taken: ≤1 year prior to screening visit • Viral load: $<4 \times 10^5$ IU/ml 57% treated patients, $>4 \times 10^5$ IU/ml 43% treated patients; not reported for control patients • ALT: normal 38%/raised 62% treated patients; not reported for control patients • Average age: ~40 years • Gender: 61% male • Genotypes: 52% 1, 48% non-1 • Mode of infection: 53% IDU, 16% transfusion, 31% unknown • Ethnicity: 90% white, 7% non-white, 3% not recorded	*Primary outcomes:* • SVR *Secondary outcomes:* • Quality of life • Adverse events

continued

TABLE 4 *Key characteristics of included studies – participants and outcomes (cont'd)*

Study	Methods	Key inclusion/exclusion criteria	Other patient characteristics	Outcomes
Zeuzem *et al.*, 2004[66]	*Design:* multicentre, open-label RCT Number of centres: 70 *Sponsor:* Roche *Country:* Australia, Europe, New Zealand, North and South America *Interventions:* PEG 2a + RBV (24 weeks) vs PEG 2a + RBV (48 weeks) vs no treatment *Follow-up:* 48 weeks (Group 1), 24 weeks (Group 2) post-treatment *No. participants:* 491	*Inclusion criteria:* • Treatment-naïve, adult patients • HCV-RNA positive • Positive antibody to HCV antibody test • Biopsy findings consistent with a diagnosis of chronic hepatitis C • Persistently normal ALT levels	• Fibrosis system: Ishak • Fibrosis stage: 69% stage 0 or 1, 20% stage 2; total mean = 1.4 • Liver biopsy taken: ≤36 months before study onset • Viral load, mean HCV RNA level: ~1190×10^3 • ALT, maximum mean: ~24 IU/l • Average age: ~43 years • Gender: 40% male • Genotypes: 68% 1, 32% non-1 • Mode of infection: 31% IDU, 23% transfusion, 14% other, 32% unknown • Ethnicity: 86% white, 8% black, 2% Asian, 4% other	*Primary outcomes:* • SVR *Secondary outcomes:* • Adverse events

TABLE 5 *Quality assessment of mild HCV trials*

Study	Randomisation	Allocation concealment	Baseline characteristics	Eligibility	Blinding of assessors	Patient blinding	Reporting outcomes	Intention-to-treat analysis	Withdrawals explained
Cheng *et al.*, 2002[67]	Par	In	Rep	Ad	In	Par	In	Ad	Ad
Chung *et al.*, 2004[68]	Un	Un	Rep	Ad	Un	NA	In	Ad	Ad
Hadziyannis *et al.*, 2004[69]	Ad	Ad	Par	Ad	Ad	Ad	Ad	Ad	Ad
Mangia *et al.*, 2001[63]	Un	Un	Rep	Ad	Un	NA	Ad	Ad	Ad
Reichard *et al.*, 1998[70]	Par	Ad	Rep	Ad	Un	Ad	In	Ad	Ad
Verbaan *et al.*, 2002[64]	Ad	Ad	Rep	Ad	In	Ad	In	Ad	Par
Wright *et al.*, 2005[65]	Un	Ad	Rep	Ad	Un	NA	In	Ad	Ad
Zeuzem *et al.*, 2004[66]	Un	Ad	Rep	Ad	Un	NA	Ad	Ad	Par

Ad. adequate; In, inadequate; NA, not applicable; Par, partial; Rep, reported; Un, unknown.

TABLE 6 *Virological response (PEG trials)*

Study **Outcome: virological response**	**Treatment arms**				
Zeuzem, 2004[66] Multicentre, open-label RCT	PEG 2a (180 µg) + RBV (800 mg), 24 weeks (n = 212)	PEG 2a (180 µg) + RBV (800 mg), 48 weeks (n = 210)	No treatment (n = 69)	Risk difference (95% CI)	RR, 48 vs 24 weeks (95% CI) + p-value[a]
% with response (95% CI): SVR at follow-up	30% (24 to 36)	52% (45 to 59)	0	22 (13 to 31)	1.7 (1.4 to 2.2) $p < 0.001$
Chung, 2004[68] Multicentre RCT HIV–HCV co-infected patients	PEG 2a + RBV 48 weeks (n = 66)			IFN 2a + RBV 48 weeks (n = 67)	p-Value[a]
% with response (n/N): SVR at follow-up	27% (18/66)	12% (8/67)			p = 0.03

[a] Between-group comparison.

HCV. The manufacturer's submission to NICE reports the SVR for the subgroup of patients with histologically mild HCV, based on Ishak fibrosis and necro-inflammation scores. This is slightly lower at 50% (n = 55/110). A further analysis supplied by the manufacturer, restricting the criteria for histologically mild HCV on baseline fibrosis score only, yielded an SVR of 51% (n = 97/188).

In the trial by Chung and colleagues,[68] treatment with PEG + RBV resulted in a significantly higher SVR than treatment with IFN + RBV. SVRs for PEG were lower than in Zeuzem and colleagues' trial.[66] This is likely to be due to co-infection with HIV.

The third PEG study, by Hadziyannis and colleagues,[69] only reported SVRs according to genotype and baseline viral load. Tabulated details can be found later in *Tables 8* and *11*. However, the authors report that PEG + RBV (standard dose 1000–12,000 mg/day) for 48 weeks produced an overall SVR of 63% (95% CI 59 to 68%).

Table 7 presents virological response rates for the five IFN trials. All trials reported significantly higher SVR rates with IFN + RBV (range 33–69%) compared with either IFN monotherapy (range 18–23%) or no treatment (zero response). Of note is the relatively high SVR of 69% achieved by patients treated with only 24 weeks of IFN + RBV in the study by Cheng and colleagues.[67] These

TABLE 7 *Virological response (IFN trials)*

Study **Outcome: virological response**	**Treatment arms**		
Cheng, 2002[67]			
Double-blind RCT	IFN 2b (6 MU) + RBV, 24 weeks (n = 26)	IFN 2b (6 MU) + placebo, 24 weeks (n = 26)	p-Value[a]
% with response (n/N):			
End of treatment	92% (24/26)	81% (21/26)	NS
SVR at follow-up	69% (18/26)	23% (6/26)	p <0.001
Mangia, 2001[63]			
Multicentre, open-label RCT	IFN 2b (5MU) + RBV (1000–1200 mg) 48 weeks (n = 96)	IFN 2b (5 MU) 48 weeks (n = 96)	p-Value[a]
% with response (95% CI):			
12 weeks	67%	43%	p = 0.001
End of treatment	59% (50 to 70)	34% (25 to 44)	p = 0.0007
SVR at follow-up	54% (44 to 64)	21% (13 to 29)	p = 0.0001
Reichard, 1998[70]	IFN 2b (3MU) + RBV	IFN 2b (3 MU) + placebo	p-Value[a]
Multicentre, double-blind RCT	(1000–1200 mg) 24 weeks (n = 50)	24 weeks (n = 50)	
% with response (n/N):			
End of treatment	52% (26/50)	52% (26/50)	p = 1.00
SVR at follow-up	36% (18/50)	18% (9/50)	p = 0.047
Verbaan, 2002[64]	IFN 2b (3 MU) + RBV	IFN 2b (3 MU) + placebo	p-Value[a]
Multicentre, double-blind RCT	(1000–1200 mg) 52 weeks (n = 57)	52 weeks (n = 59)	
% with response:			
End of treatment	49%	32%	Not reported
SVR at follow-up	54%	20%	p < 0.001
Wright, 2005[65]	IFN 2b (3 MU) + RBV	No treatment	p-Value[b]
Multicentre, open-label RCT	(1000–1200 mg) 48 weeks (n = 98)	(n = 98)	
% with response:			
End of treatment	44%	0	Not reported
SVR at follow-up	33%	0	$p \leq 0.00001$

NS, not significant.
[a] Between-group comparison.
[b] Within-group comparison.

patients were treated with a higher dose of IFN than is commonly used in practice. Also noteworthy is the relatively low SVR for patients treated with IFN + RBV in the UK RCT by Wright and colleagues.[65]

Virological response according to prognostic factors

Genotype

Sustained response rates according to genotype were reported by all the included studies, with broadly similar results (*Tables 8* and *9*).

In the trial by Zeuzem and colleagues,[66] no patient in the untreated control group cleared HCV. Across all genotypes, patients treated with PEG + RBV for 48 weeks had higher response rates than patients on the same therapy for only 24 weeks. However, this was only significant for genotype 1 patients (40 vs 13%, respectively, RR 3.1 (95% CI 1.9 to 4.9), $p < 0.001$). SVRs for patients infected with genotype 4 were similar to those infected with genotype 1. Treatment duration did not have a significant effect on virological response for patients with genotype 2

TABLE 8 *Sustained virological response according to genotype (PEG trials)*

Study **Outcome: virological response**	**Treatment arms**			
Zeuzem, 2004[66] Multicentre, open-label RCT	PEG 2a (180 μg) + RBV 24 weeks (n = 212)	PEG 2a (180 μg) + RBV 48 weeks (n = 210)	No treatment (n = 69)	RR, 48 vs 24 weeks (95% CI), p-value[a]
% with response (95% CI):				
1	13% (8 to 19)	40% (32 to 49)	0	3.1 (1.9 to 4.9), $p < 0.001$
Non-1	65%	75%	0	Not reported
2 or 3	72% (61 to 84)	78% (67 to 89)	0	1.1 (0.9 to 3.1), $p = 0.452$
4	13%	56%	0	Not reported
Hadziyannis, 2004[69] Multicentre, double-blind RCT	PEG 2a 180 μg + RBV 800 mg 24 weeks (n = 207)	PEG 2a 180 μg + RBV 1000–1200 mg 24 weeks (n = 280)	PEG 2a 180 μg + RBV 800 mg 48 weeks (n = 361)	PEG 2a 180 μg + RBV 1000–1200 mg 48 weeks (n = 436)
% with response (n/N):				
1	29% (29/101)	42% (50/119)	41% (103/250)	52% (141/271)
2 or 3	84% (81/96)	81% (117/144)	79% (78/99)	80% (122/153)
Chung, 2004[68] Multicentre RCT HIV–HCV co-infected patients	PEG 2a + RBV 48 weeks (n = 66)	IFN 2a + RBV 48 weeks (n = 67)		p-Value[a]
% with response (n/N):				
1	14% (7/51)	6% (3/52)		
Non-1	73% (11/15)	33% (5/15)		0.07

[a] Between-group comparison.

or 3 [78 vs 72% for 48 and 24 weeks, respectively, RR 1.1 (95% CI 0.9 to 3.1), $p = 0.452$]. Within treatment groups, higher SVRs were seen in genotype non-1 patients compared with genotype 1 patients, regardless of length of therapy.

In the trial by Hadziyannis and colleagues,[69] SVRs were higher for the genotype 1 patients treated for 48 weeks, and also with the 1000–1200-mg standard dose daily dose of RBV. Pooling together all genotype 1 patients treated for 48 weeks compared with all genotype 1 patients treated for 24 weeks yielded a statistically significant odds ratio (OR) in favour of 48 weeks of treatment (OR 2.19, 95% CI 1.52 to 3.16, $p < 0.0001$). SVRs for patients with genotypes 2 and 3 treated for 24 weeks were slightly higher compared with those treated for 48 weeks (OR 0.89, 95% CI 0.56 to 1.42, $p > 0.2$). Similar trends were observed in the subgroup of patients with mild baseline fibrosis (75%) (Knodell F0–F1; see *Table 16*).

In the trial of HCV–HIV co-infected patients by Chung and colleagues,[68] the SVRs for non-1 genotypes treated with PEG + RBV were broadly similar to those achieved by patients in the comparable arms of the two other PEG trials. However, for genotype 1 patients, rates were noticeably lower.

Across the genotypes, patients treated with IFN + RBV had higher SVRs than those treated with IFN monotherapy or no treatment. Furthermore, within treatment groups patients with the more favourable genotypes (i.e. genotypes 2 and 3, commonly labelled 'non-1') had higher response rates than patients with genotype 1, irrespective of treatment. Verbaan and colleagues[64] reported the largest difference (81 vs 28% and 36 vs 4% for IFN + RBV and IFN + placebo, respectively).

It should be noted that reporting of genotype groups was not consistent across trials, making comparisons difficult. Mangia and colleagues[63] have grouped genotypes 1, 4 and 5 together, compared with genotypes 2 or 3, whereas the other trials reported results for genotype 1 versus

TABLE 9 *Sustained virological response according to genotype (IFN trials)*

Study **Outcome: SVR by genotype**	**Treatment arms**			
Cheng, 2002[67] Double-blind RCT	IFN 2b (6 MU) + RBV 24 weeks (n = 26)		IFN 2b (6 MU) + placebo, 24 weeks (n = 26)	p-Value[b]
% with response (n/N): 1 Non-1	50% (7/14) 92% (11/12)[a]		27% (3/11) 20% (3/15)	<0.005
Mangia, 2001[63] Multicentre, open-label RCT	IFN 2b (5 MU) + RBV (1000–1200 mg) 48 weeks (n = 96)	p-Value[c]	IFN 2b (5 MU) 48 weeks (n = 96)	p-Value[c]
% with response (95% CI): 1, 4 or 5 2 or 3	38% (23 to 51) 69% (56 to 81)	p = 0.002	13% (4 to 21) 36% (21 to 51)	p = 0.005
Reichard, 1998[70] Multicentre, double-blind RCT	IFN 2b (3 MU) + RBV (1000–1200 mg) 24 weeks (n = 50)		IFN 2b (3 MU) + placebo 24 weeks (n = 50)	p-Value[b]
% with response (n/N): 1a 1b 1 not subtyped/1a + b 2 3a	36% (4/11) 13% (1/8) 0/3 43% (3/7) 53% (10/19)		17% (1/6) 9% (1/11) 0/5 25% (3/12) 21% (3/14)	p = 0.60 p = 1.00 p = 0.62 p = 0.09
Verbaan, 2002[64] Multicentre, double-blind RCT	IFN 2b (3 MU) + RBV (1000–1200 mg) 52 weeks (n = 57)		IFN 2b (3 MU) + placebo 52 weeks (n = 59)	p-Value[b]
% with response: 1 Non-1	28% 81%		4% 36%	p = 0.014 p = 0.003
Wright, 2005[65] Multicentre, open-label RCT	IFN 2b (3 MU) + RBV 48 weeks (n = 98)		No treatment (n = 98)	p-Value[c]
% with response: 1 Non-1	18% 49%		0 0	p = 0.02

[a] $p < 0.05$ for comparison with genotype 1.
[b] Between-group comparison.
[c] Within-group comparison (favourable versus unfavourable baseline features in each treatment group).

non-1. Zeuzem and colleagues[66] reported genotypes 2 or 3 and 4, separately.

Viral load

Four trials, all of IFN, reported SVR as a function of baseline viral load, stratified into low or high viral titres (*Table 10*). In general, patients receiving combination therapy were more likely to achieve an SVR compared with patients receiving IFN monotherapy or no treatment, regardless of baseline viral load. However, within the treatment groups results were mixed. In two studies[63,65] baseline viraemia did not significantly influence the rate of sustained virological response. However, in another study,[67] SVRs were significantly higher for patients with low baseline viraemia.

The trial by Verbaan and colleagues[64] reports geometric mean viral load (equivalent genomes per millilitre) for sustained responders and non-responders within each treatment arm (IFN + RBV vs IFN + placebo), rather than the proportion of patients with low/high viraemia who achieved a response. This study found that in the combination therapy group, mean

TABLE 10 *Sustained virological response according to baseline viral load (IFN trials)*

Study **Outcome: SVR by viral load**	**Treatment arms**			
Cheng, 2002[67] Double-blind RCT	IFN 2b (6 MU) + RBV 24 weeks (n = 26)		IFN 2b (6 MU) + placebo 24 weeks (n = 26)	p-Value[a]
% with response (n/N): ≤3 Milliequivalents/ml >3 Milliequivalents/ml	92% (12/13)[b] 46% (6/13)		50% (6/12)[c] 0 (0/14)	<0.05 <0.005
Mangia, 2001[63] Multicentre, open-label RCT	IFN 2b (5 MU) + RBV (1000–1200 mg) 48 weeks (n = 96)	p-Value[d]	IFN 2b (5 MU) 48 weeks (n = 96)	p-Value[d]
% with response (95% CI): Low[e] High[e]	49% (32 to 64) 58% (45 to 70)	p = 0.39	26% (13 to 40) 21% (10 to 31)	p = 0.52
Reichard, 1998[70] Multicentre, double-blind RCT	IFN 2b (3 MU) + RBV (1000–1200 mg) 24 weeks (n = 50)		IFN 2b (3 MU) + placebo 24 weeks (n = 50)	p-Value[a]
% with response (n/N): $<1 \times 10^6$ $1–2.99 \times 10^6$ $3–7.99 \times 10^6$ $8–19.99 \times 10^6$ $\geq 20 \times 10^6$	45% (5/11) 10% (1/10) 10% (1/10) 62% (8/13) 50% (3/6)		45% (5/11) 23% (3/13) 0/13 13% (1/8) 0/5	1.00 0.60 1.00 0.07 0.18
Wright, 2005[65] Multicentre, open-label RCT	IFN 2b (3 MU) + RBV 48 weeks (n = 98)		No treatment (n = 98)	p-Value[d]
% with response: $<4 \times 105$ IU/ml[f] $>4 \times 105$ IU/ml[f]	34% 31%		0 0	p = 0.82

[a] Between-group comparison.
[b] $p < 0.05$ for comparison with HCV RNA level >3 MEq/ml.
[c] $p < 0.005$ for comparison with HCV RNA level >3 MEq/ml.
[d] Within-group comparison (favourable versus unfavourable baseline features in each treatment group).
[e] Low viraemia ≤200,000 equivalent genomes/ml, high viraemia ≥200,000 equivalent genomes/ml.
[f] 1 IU is equivalent to approximately 5 RNA copies.

viral load was lower among sustained responders compared with non-responders (4.6×10^5 vs 2.0×10^6, respectively, $p = 0.034$). The same tendency was seen within the IFN + placebo monotherapy group between sustained responders and those who did not clear the infection (5.9×10^5 vs 2.4×10^6, respectively, $p = 0.002$).

It is worth noting that the studies differed in terms of the measurement of viral load, with the Mangia[63] and Verbaan[64] trials presenting viral load in equivalent genomes/ml, the Zeuzem[66] and Wright[65] trials reporting IU/mL and the Cheng[67] and Reichard[70] trials reporting MEq/Eq per ml.

Combined genotype and viral load

Three trials reported SVRs according to a combination of baseline genotype and baseline viral load. Results are presented in *Tables 11* and *12*.

In the PEG study by Zeuzem and colleagues,[66] baseline viral load [high viral load vs low viral load: OR, 2.21 (95% CI 1.20 to 4.09)] significantly affected SVRs in patients with genotype 1. In genotype 1 patients with a low baseline viral load, the unadjusted probability of achieving an SVR was 77% higher than in patients with a high viral load (unadjusted RR 1.77, 95% CI 1.12 to 2.82). In contrast, baseline viral load did not have a significant effect on SVRs in patients infected with

TABLE 11 *Sustained virological response according to combined genotype and viral load (PEG trials)*

Study **Outcome: SVR by genotype + viral load**	**Treatment arms**			
Zeuzem, 2004[66] Multicentre, open-label RCT	PEG 2a (180 μg) + RBV 24 weeks (n = 212)	PEG 2a (180 μg) + RBV 48 weeks (n = 210)	No treatment (n = 69)	
% with response:				
Genotype 1:				
Low viral load[a]	16%	47%	0	
High viral load[a]	9%	27%	0	
Genotype non-1:				
Low viral load[a]	69%	79%	0	
High viral load[a]	59%	71%	0	
Genotype 2 or 3:				
Low viral load[a]	80%	81%	0	
High viral load[a]	64%	75%	0	
Genotype 4:				
Low viral load[a]	17%	67%	0	
High viral load[a]	0	33%	0	
Hadziyannis, 2004[69] Multicentre, double-blind RCT	PEG 2a 180 μg + RBV 800 mg 24 weeks (n = 207)	PEG 2a 180 μg + RBV 1000–1200 mg 24 weeks (n = 280)	PEG 2a 180 μg + RBV 800 mg 48 weeks (n = 361)	PEG 2a 180 μg + RBV 1000–1200 mg 48 weeks (n = 436)
% with response (n/N):				
Genotype 1:				
Low viral load[b]	41% (21/51)	52% (37/71)	55% (33/60)	65% (55/85)
High viral load[b]	16% (8/50)	26% (12/47)	36% (68/190)	47% (88/186)
Genotype 2 or 3:				
Low viral load[b]	85% (29/34)	83% (39/47)	88% (29/33)	77% (37/48)
High viral load[b]	84% (52/62)	80% (78/97)	74% (49/66)	82% (86/105)

[a] Low viral load ≤800,000 IU/ml, high viral load >800,000 IU/ml.
[b] Low viral load ≤2×10^6 copies/ml; high viral load >2×10^6 copies/ml.

non-1 genotypes, although viral load did appear to influence SVRs in patients infected with genotype 4.

In the trial by Hadziyannis and colleagues,[69] genotype 1 patients with low viral load achieved higher SVRs than those with high viral load. Notably, the SVR for patients with low viral load treated for 24 weeks with the standard dose of ribavirin was almost as high as that for patients treated for 48 weeks with a lower ribavirin dose. Pooling together all genotype 1 patients treated for 48 weeks compared with all those treated for 24 weeks yielded a statistically significant OR in favour of 48 weeks of treatment (low viral load, OR 1.71, 95% CI 1.05 to 2.80, $p = 0.034$; high viral load, OR 2.90, 95% CI 1.66 to 5.07, $p = 0.0001$). In genotype 2 and 3 patients there was little additional benefit in extending treatment to 48 weeks (OR 0.89, 95% CI 0.56 to 1.42, $p > 0.2$).

In the trial by Mangia and colleagues,[63] response rates for IFN + RBV therapy were higher than for IFN monotherapy regardless of the viral load or genotype. Within the combination treatment group, SVRs were similar irrespective of the level of viraemia [p = not significant (NS)], although SVRs were twice as high for patients with genotype 2 or 3 compared with genotype 1, 4 or 5 for both low and high viral load.

ALT level

Only one study[65] reported SVR according to baseline ALT levels (*Table 13*). Approximately one-third of patients receiving IFN + RBV combination therapy achieved a sustained response compared with zero patients receiving no treatment. Within the combination therapy group, baseline ALT levels (raised or normal) did not have a significant effect on SVRs.

Age

Table 14 shows SVRs according to age, stratified into age less than or greater than 40 years. In the two trials where data are presented,[63,65] patients

TABLE 12 *Sustained virological response according to combined genotype and viral load (IFN)*

Study **Outcome: SVR by genotype + viral load**	**Treatment arms**			
Mangia, 2001[63] Multicentre, open-label RCT	IFN 2b (5 MU) + RBV (1000–1200 mg) 48 weeks (n = 96)	p-Value[a]	IFN 2b (5 MU) 48 weeks (n = 96)	p-Value[a]
% with response (95% CI):				
Genotype 1, 4, 5				
Low viraemia[b]	32% (12 to 51)	p = 0.83	17% (17 to 31)	p = 0.22
High viraemia[b]	35% (15 to 54)		7% (0 to 9)	
Genotype 2, 3:				
Low viraemia[b]	71% (48 to 92)	p = 0.82	27% (4 to 49)	p = 0.36
High viraemia[b]	74% (59 to 88)		41% (22 to 59)	

[a] Within-group comparison (favourable versus unfavourable baseline features in each treatment group).
[b] Low viraemia ≤200,000 equivalent genomes/ml, high viraemia ≥200,000 equivalent genomes/ml.

TABLE 13 *Sustained virological response according to ALT level*

Study **Outcome: SVR by ALT**	**Treatment arms**		
Wright, 2005[65] Multicentre, open-label RCT	IFN 2b (3 MU) + RBV 48 weeks (n = 91)	No treatment (n = 98)	p-Value[a]
% with response:			
Normal	34%	0	p = 0.92
Raised	36%	0	

[a] Within-group comparison (favourable versus unfavourable baseline feature in treatment group).

receiving combination therapy had higher SVRs than those receiving monotherapy or no treatment, regardless of age. In both trials age did not significantly influence the rate of sustained response within treatment groups.

Zeuzem and colleagues[66] also examined the effect of age on SVR rates but stratified the analysis by HCV genotype (1 vs non-1) (not shown in the table). Age was significantly associated with SVRs in patients with genotype non-1 [≤40 years vs >40 years: OR 2.31 (95% CI 1.02 to 5.24)]. Younger patients (≤40 years) had a 26% higher probability of achieving an SVR compared with patients aged >40 years [RR, 1.26 (95% CI 1.02 to 1.55)].

Gender

Sustained virological response rates according to gender are presented in *Table 15*. Within treatment groups, the rate of sustained response was similar for both males and females in both trials.

Histology

Two trials reported SVRs according to baseline liver histology (*Tables 16* and *17*).

Hadziyannis and colleagues[69] stratified SVRs by baseline fibrosis (scored using the Knodell system) and genotype. In general, SVRs were higher in patients with mild HCV (F0 or F1) compared with those with bridging fibrosis/cirrhosis (F3 or F4). Caution is advised as the number of patients in the F3/F4 category was relatively small (25%). SVRs in patients with mild HCV were similar to those reported for all patients regardless of baseline fibrosis score (see *Table 8*), that is, generally higher SVRs for genotype 1 patients treated for 48 weeks and with a standard dose of RBV and a net loss of benefit when treating genotype 2 and 3 patients for 48 weeks and with a standard RBV dose.

Mangia and colleagues[63] reported SVRs according to baseline fibrosis stage (stage 0 or 1 vs >1) and necro-inflammation grade (grade 1 or

TABLE 14 *Sustained virological response according to age (IFN)*

Study **Outcome: SVR by age**	**Treatment arms**			
Mangia, 2001[63] Multicentre, open-label RCT	IFN 2b (5 MU) + RBV (1000–1200 mg) 48 weeks (n = 96)	p-Value[a]	IFN 2b (5MU) 48 weeks (n = 96)	p-Value[a]
% with response (95% CI): ≤40 years >40 years	61% (44 to 77) 51% (38 to 63)	p = 0.35	15% (20 to 27) 27% (16 to 37)	p = 0.19
Wright, 2005[65] Multicentre, open-label RCT	IFN 2b (3 MU) + RBV 48 weeks (n = 91)		No treatment (n = 98)	p-Value[a]
% with response: <40 years >40 years	38% 32%		0 0	p = 0.65

[a] Within-group comparison (favourable versus unfavourable baseline features in each treatment group).

TABLE 15 *Sustained virological response according to gender*

Study **Outcome: SVR by gender**	**Treatment arms**			
Mangia, 2001[63] Multicentre, open-label RCT	IFN 2b (5 MU) + RBV (1000–1200 mg) 48 weeks (n = 96)	p-Value[a]	IFN 2b (5 MU) 48 weeks (n = 96)	p-Value[a]
% with response (95% CI): Male Female	55% (43 to 66) 52% (33 to 71)	p = 0.77	24% (13 to 34) 22% (8 to 35)	p = 0.54
Wright, 2005[65] Multicentre, open-label RCT	IFN 2b (3 MU) + RBV 48 weeks (n = 91)		No treatment (n = 98)	p-Value[a]
% with response: Male Female	39% 28%		0 0	p = 0.47

[a] Within-group comparison (favourable versus unfavourable baseline features in each treatment group).

2 vs 3), scored using the Scheuer criteria (*Table 17*). The histological staging significantly affected the sustained response in the combination therapy group, with SVRs being more than two times higher in patients with a lower fibrosis stage compared with a higher stage (63 vs 28% respectively, p = 0.004).

Biochemical response (ALT)

Three trials, all IFN, reported ALT response rates following treatment (*Table 18*).

Response was measured by reduction in ALT to normal levels. In all trials, response rates subsided between end of treatment and follow-up. Both end of treatment and follow-up rates were significantly greater for IFN + RBV compared with IFN monotherapy or IFN with placebo. The magnitude of response varied according to dose and regimen.

In the trial by Mangia and colleagues,[63] the combined biochemical and virological response rate was more than 2.5 times higher (p < 0.0001) in patients receiving IFN + RBV compared with patients receiving IFN alone. At the end of follow-up, normalisation of ALT values was associated with undetectable levels of serum

TABLE 16 *Sustained virological response according to baseline liver histology (PEG)*

Study **Outcome: SVR by histology**	**Treatment arms**			
Hadziyannis, 2004[69] Multicentre, double-blind RCT	PEG 2a 180 μg + RBV 800 mg 24 weeks (*n* = 207)	PEG 2a 180 μg + RBV 1000–1200 mg 24 weeks (*n* = 280)	PEG 2a 180 μg + RBV 800 mg 48 weeks (*n* = 361)	PEG 2a 180 μg + RBV 1000–1200 mg 48 weeks (*n* = 436)
% with response (*n*/*N*):				
F3 or F4, genotype 1	26% (6/23)	26% (7/27)	28% (19/67)	41% (32/78)
F3 or F4, genotype 2 or 3	75% (15/20)	74% (29/39)	70% (14/20)	73% (24/33)
F0 or F1, genotype 1	29% (23/78)	46% (42/91)	45% (83/183)	57% (110/193)
F0 or F1, genotype 2 or 3	87% (66/76)	84% (88/105)	81% (64/79)	83% (100/120)

F0 or F1, mild fibrosis; F3, bridging fibrosis; F4, cirrhosis (Knodell classification system).

TABLE 17 *Sustained virological response according to baseline liver histology (IFN)*

Study **Outcome: SVR by histology**	**Treatment arms**			
Mangia, 2001[63] Multicentre, open-label RCT	IFN 2b (5 MU) + RBV (1000–1200 mg) 48 weeks (*n* = 96)	*p*-Value[a]	IFN 2b (5 MU) 48 weeks (*n* = 96)	*p*-Value[a]
% with response (95% CI):				
Fibrosis stage:				
0 or 1	63% (52 to 74)	$p = 0.004$	19% (10 to 28)	$p = 0.10$
>1	28% (10 to 45)		37% (15 to 58)	
Necro-inflammation grade:				
1 or 2	20% (11 to 28)	$p = 0.14$	53% (43 to 63)	$p = 0.52$
3	40% (19 to 80)		67% (28 to 104)	

[a] Within-group comparison (favourable versus unfavourable baseline features in treatment group).

HCV RNA in 71 out of 72 patients (98.6%) who had an SVR. Serum HCV RNA levels remained detectable after treatment, despite persistently normal serum ALT concentration, in five out of 77 patients (6.5%), of whom three were on combination therapy and two on IFN monotherapy.

Histological response

Histological response rates were reported in four RCTs and are presented in *Tables 19* and *20*.

Chung and colleagues[68] reported histological response for patients who achieved a virological response at week 24 and for those who did not. Just over half of the virological responders who underwent a biopsy were classed as histological improvers. Just over one-third of virological non-responders who underwent biopsy achieved a histological response.

Three of the IFN trials reported changes in liver histology. There were no significant changes in fibrosis scores. In the trial by Verbaan and colleagues[64] for patients with a sustained response there was a significant improvement ($p \leq 0.018$) in mean inflammation grade score irrespective of the treatment group. There was no significant change in non-responders. Verbaan and colleagues[64] also reported that the low fibrosis stage (mean stage 0.3 and 0.4 for IFN + RBV and IFN + placebo groups, respectively) did not change in either group, irrespective of treatment results, but data are not presented.

Health-related quality of life

Fully published data on the impact of treatment on HRQoL are available for only one of the eight RCTs, the UK mild HCV trial[65] (a conference abstract reports data for another trial; see below). The study compared IFN + RBV with no

TABLE 18 *Biochemical response (ALT normalisation)*

Study **Outcome: biochemical response**	**Treatment arms**		
Cheng, 2002[67] Double-blind RCT	IFN 2b (6 MU) + RBV 24 weeks (n = 26)	IFN 2b (6 MU) + placebo 24 weeks (n = 26)	p-Value[a]
% with response (n/N): End of treatment End of follow-up	 92% (24/26) 65% (17/26)	 81% (21/26) 19% (5/26)	 NS <0.001
Mangia, 2001[63] Multicentre, open-label RCT	IFN 2b (5 MU) + RBV (1000–1200 mg) 48 weeks (n = 96)	IFN 2b (5 MU) 48 weeks (n = 96)	p-Value[a]
% with response (95% CI): End of treatment (12 months) End of follow-up (6 months)	 69% (60 to 70) 57% (48 to 67)	 40% (30 to 49) 23% (15 to 31)	 p = 0.0001 p = 0.0001
Combined sustained biochemical and virological response	61% (50 to 71)	23% (14 to 31)	p < 0.0001
Reichard, 1998[70] Multicentre, double-blind RCT	IFN 2b (3 MU) + RBV (1000–1200 mg) 24 weeks (n = 50)	IFN 2b (3 MU) + placebo 24 weeks (n = 50)	p-Value[a]
% with response (n/N): End of treatment End of follow-up	 66% (33/50) 44% (22/50)	 56% (28/50) 24% (12/50)	 p = 0.41 p = 0.057

[a] Between-group comparison.

TABLE 19 *Histological response (PEG)*

Study **Outcome: histological response**	**Treatment arms**		
Chung, 2004[68] Multicentre RCT HIV–HCV co-infected patients	PEG 2a + RBV 48 weeks (n = 66)		IFN 2a + RBV 48 weeks (n = 67)
No virological response at week 24: Histologic response	(n = 37) 9/26[a] (35%)		(n = 57) 16/45[a] (36%)
Virological response at week 24: Histological improvement No change Worsening disease		(n = 39) 14/27[b] (52%) 11/27[b] (41%) 2/27[b] (7%)	

[a] 26 of 37 patients underwent liver biopsy, 45 of 57 patients underwent liver biopsy.
[b] 27 of 39 patients underwent liver biopsy at week 48.

treatment. HRQoL was measured using the SF-36, a generic health status survey of general health items.

The SF-36 questionnaire was completed by participants at baseline and at 24 weeks post-treatment cessation, and their responses to eight concepts were reported in addition to summary physical component scores (PCSs) and mental component scores (MCSs). The eight concepts were physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. Differences between baseline and post-week 24 scores for the eight concept scales and two summary scales were compared across three groups: SVRs, treatment failures (non-SVRs), including non-responders and relapsed patients, and the control group. Data

TABLE 20 *Histological response (IFN trials)*

Study **Outcome: histological response**	**Treatment arms**			
Cheng, 2002[67] Double-blind RCT	IFN 2b (6 MU) + RBV 24 weeks (n = 26)		IFN 2b (6 MU) + placebo 24 weeks (n = 26)	p-Value[a]
Histological improvement (n = 48):				
Inflammation, mean decrease ± SD	1.3 ± 0.5		1.3 ± 0.5	p = 0.27
Fibrosis, mean decrease ± SD	0.8 ± 3.3		0.0 ± 2.1	
Reichard, 1998[70] Multicentre, double-blind RCT	IFN 2b (3 MU) + RBV (1000–1200 mg) 24 weeks (n = 50)		IFN 2b (3 MU) + placebo 24 weeks (n = 50)	p-Value[a]
Mean inflammation grade score (SD):				
Before treatment	1.4 (0.5)		1.3 (0.5)	p < 0.001
End of treatment	0.9 (0.5)		0.8 (0.7)	
Mean fibrosis stage score	No change		No change	
Verbaan, 2002[64] Multicentre, double-blind RCT	IFN 2b (3 MU) + RBV (1000–1200 mg) 52 weeks (n = 45)	p-Value[b]	IFN 2b (3 MU) + placebo 52 weeks (n = 36)	p-Value[b]
Mean inflammation grade:				
Sustained responders:	(n = 30)		(n = 9)	
At entry	4.3		4.1	
At follow-up (26 weeks)	1.3	p < 0.018	1.3	p = 0.018
Non-responders:	(n = 15)		(n = 27)	
At entry	3.4		4.4	
At follow-up (26 weeks)	3.5	p = NS	4.9	p = NS

[a] Between-group comparison.
[b] Within-group comparison (at entry versus follow-up).

were available for 75% of the SVRs, 65% of the non-SVRs and approximately half (56%) of the control group.

At 24 weeks after the end of treatment, there was a mean improvement from baseline in 7/8 of the SF-36 subscales in the SVRs, with a significant improvement seen for bodily pain, general health and vitality (p = 0.01 compared with controls). Mean improvements were also observed in 5/8 subscales in non-SVRs. In contrast, reductions were seen in all eight of the SF-36 subscales in the control group. In the SVR group, there was an overall deterioration in only one subscale (role function emotional) which was significantly different to the improvement seen in the non-SVRs (p < 0.05).

Similarly, the mean change in the PCS and MCS scores showed improvements in the SVR and non-SVR groups with deterioration in the controls. Similar proportions of patients in the SVR (67%) and non-SVR (61%) groups reported an improvement in the PCS scores compared with 41% of controls (p < 0.05). There were no statistical differences in the MCS scores. The mean changes in PCS and MCS scores varied substantially in both magnitude and direction of change from baseline to 24 weeks post-treatment. Despite this, the mean change in PCS was significantly greater in the SVRs compared with the controls (p = 0.04).

There were significant inverse correlations between baseline PCS and the change in PCS in both the SVRs (R = –0.46, p = 0.02) and non-SVRs (R = –0.45, p = 0.002), but not the controls. This suggests that individuals with low well-being scores prior to treatment saw a sustained improvement 24 weeks after therapy, regardless of virological outcome. In contrast, patients with preserved baseline well-being scores experienced no long-term improvement.

In addition, HRQoL data from Zeuzem and colleagues' trial of PEG were presented in a conference abstract.[71] As these data have not yet

been fully published, and therefore not subjected to appraisal, caution is advised in their interpretation. Briefly, the key findings were:

- Responders had better SF-36 and Fatigue Severity Scale (FSS) scores than non-responders and untreated controls.
- Differences between responders and non-responders were statistically significant for SF-36 domains of general health, pain index, role physical, social function, vitality and physical component scores and for FSS.
- Differences between responders and untreated controls were statistically significant in general health and vitality.

Adverse events

Adverse events for the five IFN trials and three PEG trials are presented in *Table 21*. The incidence of any dose discontinuations due to adverse events was reported by all eight trials and was similar across treatment groups (range 8–17%) for the five IFN trials and the PEG trial by Chung and colleagues.[68] For the other two PEG trials,[66,69] there was larger variation between treatment groups (range 7–57%). In both studies, the highest proportion of patients who had to stop treatment due to adverse events occurred in those receiving PEG + RBV for the longer duration of 48 weeks (range 18–57%), and was two to four times the incidence in patients receiving the same treatment for 24 weeks (range 7–12%).

For the five IFN trials, the incidence of drug dose modifications was higher in the combination treatment group compared with IFN monotherapy. This suggests that some adverse events were due to RBV, which is not unexpected. In Mangia and colleagues' trial,[63] it is unclear how many patients in total required a dose modification, although the authors do report that 12 patients (13%) in the dual therapy group required a reduction in the dose of RBV, and that 44 patients (23%) in total had to switch from recombinant IFN 2b to natural leucocyte IFN due to hard to tolerate side-effects, but numbers were not provided for individual treatment groups. In two PEG trials,[66,69] patients treated for 24 weeks had a lower incidence of dosage reductions due to adverse events or laboratory abnormalities than those treated for 48 weeks. In the third PEG trial, comparing PEG and IFN in HIV–HCV co-infected patients,[68] the proportion requiring a dose modification was much smaller and was similar between treatment groups (5 vs 4% respectively).

Three trials[64,65,68] reported the number of patients hospitalised during the treatment period, and the number was very small in all three studies (seven patients in total). In two trials, the hospitalisations occurred in patients in the combination therapy groups only; Chung and colleagues[68] did not specify the treatment group to which the patients belonged. Five of the hospitalisations were unrelated to treatment. Similarly, few deaths were reported (nine deaths in four studies[65,66,68,69]), seven of which were unrelated to treatment.

The trials varied substantially both in the way in which adverse events were reported and in the detail of the reporting. Some differences included reporting:

- the number of adverse events occurring in patients
- the number of patients affected by each adverse event
- the number of patients experiencing at least one adverse event
- adverse events occurring in, for example, >5% of the patient population
- the total number of adverse events or patients affected but not differentiating between treatment groups
- categorising adverse events into moderate/severe/life-threatening, and further categorising into events occurring in weeks 0–24 and weeks 25–72.

These differences make comparisons between studies difficult. However, most adverse events reported in treated patients were typical of those commonly associated with IFN-based treatment. The most frequently occurring adverse events were the same in all the trials, and included influenza-like symptoms such as headache, fatigue, fever and myalgia. Depression also occurred fairly commonly, as reported in all but one of the trials.[63] It is unclear whether the 'mild neuropsychiatric effects' reported by Mangia and colleagues[63] included depression. Adverse events were generally mild[66] or mild–moderate[64,69] in severity as reported by three trials.

Only two trials[67,70] reported statistical tests for comparison between groups. Cheng and colleagues[67] reported a higher incidence of adverse events in combination therapy patients compared with monotherapy patients, being statistically significant for anorexia and insomnia ($p < 0.05$). Reichard and colleagues[70] reported that nausea occurred in significantly more combination therapy patients compared with

TABLE 21 *Adverse events*

Reported adverse events: *n* (%) of patients affected	IFN trials									
	Cheng *et al.*, 2002[67]		Mangia *et al.*, 2001[63]		Reichard *et al.*, 1998[70]		Verbaan *et al.*, 2002[64]		Wright *et al.*, 2005[65]	
	IFN 2b (6 MU) + RBV (*n* = 26)	IFN 2b (6 MU) + placebo (*n* = 26)	IFN 2b (5 MU) + RBV (*n* = 96)	IFN 2b (5 MU) (*n* = 96)	IFN 2b (3 MU) + RBV (*n* = 50)	IFN 2b (3 MU) + placebo (*n* = 50)	IFN 2b (3 MU) + RBV (*n* = 57)	IFN 2b (3 MU) + placebo (*n* = 59)	IFN 2b (3 MU) + RBV (*n* = 98)	No treatment (*n* = 98)
Discontinuation of treatment:										
Serious adverse event							3 (5)	0	0	NA
Adverse event	1 (4)	0	10 (10)	8 (8)	4 (8)	3 (6)	3 (5)	3 (5)	10 (10)	NA
Other reason	1 (4)	0			3 (6)		2 (4)	7 (12)	0	NA
Dose modification:										
Anaemia	6 (23)	0	12 (13)		1 (2)	0	4 (7)	0	30 (31)	NA
Adverse event[a]					7 (14)	0	9 (16)	2 (3)	16 (16)	NA
Laboratory abnormality/other reason	6 (23)	8 (31)			1 (2)	3 (6)	1 (2)	0	0	NA
Hospitalisations	NR	NR	NR	NR	NR	NR	2 (4)	0	4 (4)	0
Deaths	NR	NR	NR	NR	NR	NR	NR	NR	3 (3)	0
Any adverse event[b,c]	NR	NR	NR	NR	NR	NR	104 (90)[d]		770	257
Severe adverse event	NR	NR	NR	NR	NR	NR				
Serious adverse event	NR	NR	NR	NR	NR	NR				

	PEG IFN trials								
	Chung *et al.*, 2004[68]		Hadziyannis *et al.*, 2004[69]					Zeuzem *et al.*, 2004[66]	
	PEG 2a (180 μg) + RBV (*n* = 66)	IFN 2a (3–6 MIU) + RBV (*n* = 67)	PEG 2a (180 μg) + RBV 800 mg 24 weeks (*n* = 207)	PEG 2a (180 μg) + RBV 1000–1200 mg 24 weeks (*n* = 280)	PEG 2a (180 μg) + RBV 800 mg 48 weeks (*n* = 361)	PEG 2a (180 μg) + RBV 1000–1200 mg 48 weeks (*n* = 436)	PEG 2a (180 μg) + RBV 24 weeks (*n* = 212)	Peg 2a (180 μg) + RBV 48 weeks (*n* = 210)	No treatment (*n* = 69)
Discontinuation of treatment:									
Serious adverse event									NA
Adverse event[e]	8 (12)	8 (12)	10 (5)	13 (5)	59 (16)	67 (15)	15 (7)	38 (18)	NA
Other reason			14 (7)	22 (8)	148 (41)	141 (32)			NA

continued

TABLE 21 *Adverse events (cont'd)*

	PEG IFN trials								
	Chung *et al.*, 2004[68]		Hadziyannis *et al.*, 2004[69]					Zeuzem *et al.*, 2004[66]	
	PEG 2a (180 μg) + RBV (*n* = 66)	IFN 2a (3–6 MIU) + RBV (*n* = 67)	PEG 2a (180 μg) + RBV 800 mg 24 weeks (*n* = 207)	PEG 2a (180 μg) + RBV 1000–1200 mg 24 weeks (*n* = 280)	PEG 2a (180 μg) + RBV 800 mg 48 weeks (*n* = 361)	PEG 2a (180 μg) + RBV 1000–1200 mg 48 weeks (*n* = 436)	PEG 2a (180 μg) + RBV 24 weeks (*n* = 212)	PEG 2a (180 μg) + RBV 48 weeks (*n* = 210)	No treatment (*n* = 69)
Dose modification:									
Anaemia									NA
Adverse event[d]	3 (5)	3 (4)	102 (49)	149 (53)	221 (61)	325 (74)	65 (31)	102 (49)	NA
Laboratory abnormality/other reason							52 (25)	92 (44)	NA
Hospitalisations	1 (<1)[f]		NR	NR	NR	NR	NR	NR	NR
Deaths	1 (<1)[f]		0	1 (<1)	1 (<1)	2 (<1)	0	0	1 (1)
Any adverse event[c]:	NR	NR					209 (99)	207 (99)	53 (77)
Severe adverse event	NR	NR	46 (22)	63 (23)	116 (32)	141 (32)	56 (26)	70 (33)	10 (14)
Serious adverse event	NR	NR	7 (3)	19 (7)	33 (9)	44 (10)	18 (8)	34 (16)	4 (6)

NA, not applicable; NR, not reported.

[a] In the Mangia trial,[63] 44/192 patients (23%) switched from recombinant IFN 2b to natural leucocyte IFN due to hard to tolerate side-effects – numbers were not provided for individual treatment groups.

[b] Number of events (rather than number of patients affected) in the Wright trial.[65]

[c] In the Cheng,[67] Reichard[70] and Chung[68] trials, specific adverse events were reported for each treatment group, but not the total number of patients who had an adverse event or the total number of adverse events.

[d] *n* (%) of patients who reported at least one adverse event; numbers not stated for individual treatment groups.

[e] Adverse event included laboratory abnormalities in all three PEG trials.[66,68,69]

[f] Did not specify which treatment group.

monotherapy ($p = 0.02$). In addition, the total number of patients requiring dose discontinuation or reduction was also significantly greater in the IFN + RBV group ($p = 0.03$).

In both the Wright and Zeuzem trials,[65,66] the levels of most adverse events were higher in the treatment groups compared with no treatment, as would be expected. For the two IFN trials where specific adverse events were listed,[65,67] the incidence of events in the combination therapy group appeared generally higher compared with monotherapy. For the other three IFN trials,[63,64,70] the authors reported that events did not differ between treatment groups. In the two PEG trials comparing treatment duration,[66,69] levels of adverse events were similar between the two treatment groups for the majority of events, although in Zeuzem and colleagues' trial[66] patients who received PEG + RBV for the shorter duration of 24 weeks faired mildly better than those treated for 48 weeks. In the smaller PEG trial, the incidence of adverse events did not appear to differ between patients treated with PEG compared with IFN dual therapy, although no statistical significance values were reported.

Clinical effectiveness: summary

- All five IFN trials reported significantly higher SVR rates with IFN + RBV combination therapy compared with either IFN monotherapy or no treatment. Treatment with PEG dual therapy resulted in a significantly higher SVR than treatment with IFN dual therapy. PEG combination treatment for 48 weeks was significantly more effective than the same treatment for 24 weeks.
- Patients with non-1 genotype had higher virological response rates than patients with genotype 1. Genotype 1 patients had significantly higher SVR rates when treated for 48 weeks compared with 24 weeks. Combined genotype 1 and low baseline viral load (two PEG trials), and also combined genotype non-1 and lower age (one PEG trial), were also significantly associated with SVR. In addition, two trials found that a lower baseline fibrosis stage (stage 0 or 1) was associated with a higher sustained response. In only one of these was the difference reported to be significant.
- In two IFN trials, the rate of biochemical response (reduction of ALT to normal levels) at the end of treatment was significantly higher among patients taking IFN + RBV compared with IFN alone. Similarly, the combined rate of sustained biochemical and virological response was more than 2.5 times higher in patients receiving IFN dual therapy compared with patients receiving IFN alone.
- Two IFN trials found a significant improvement in mean inflammation grade score between entry and follow-up in patients with a sustained response, for both IFN combination therapy and monotherapy treatment groups.
- There were significant improvements in quality of life from baseline to 24 weeks post-treatment in patients treated with IFN + RBV compared with those who received no treatment.
- The most frequently occurring adverse events were similar across the trials, and included influenza-like symptoms such as headache, fatigue, fever and myalgia. Depression also occurred fairly commonly.
- The incidence of adverse events did not differ greatly between treatment groups, although in two trials the incidence was higher in the treatment groups compared with no treatment, as would be expected. In two PEG trials, the incidence of dose modifications and discontinuations were higher in patients treated for 48 weeks compared with those treated for 24 weeks.

Monotherapy trials

In addition to the dual therapy trials reviewed in the previous section, two monotherapy trials were included. These were both reported in the previous assessment report, but also met the criteria for the current report as the majority of patients were classed as having mild HCV according to liver biopsy. Full data extraction and critical appraisal details can be found in Appendices 16 and 17. Below is a brief description of their key characteristics and results.

Reddy and colleagues[72] randomised 159 patients to IFN 2a monotherapy ($n = 33$) or to three ascending doses of PEG 2a monotherapy (45 µg $n = 20$; 90 µg, $n = 20$; 180 µg, $n = 45$; or 270 µg, $n = 41$). At baseline 144 (91%) of the patients were classed as 'non-cirrhosis' (≤F2), and 15 (9%) were classed as having bridging fibrosis, according to the Ishak biopsy classification system. The majority of patients had genotype 1 (74%). Only 3% of patients receiving IFN monotherapy had an SVR, compared with 10–29% of patients receiving various doses of PEG monotherapy (statistically significant for all comparisons with IFN monotherapy). SVRs increased in a dose-dependent manner between 45 and 180 µg with no further increase in response at the 270-µg dose. SVRs were higher in the subgroup of patients with genotypes non-1. Rates reached as

high as 67% for both the 90- and 270-µg PEG dose groups.

Lindsay and colleagues[73] randomised patients to IFN 2b (n = 303) or to three doses of PEG 2b (0.5 µg/kg, n = 315; 1.0 µg/kg, n = 297; 1.5 µg/kg, n = 304). This was an international multicentre RCT conducted in the USA, Europe and Australia. At baseline 164 (13%) of the patients were classified as having bridging fibrosis (F3) and 4% as having cirrhosis, according to the Knodell classification system. The mean fibrosis score was 1.4. According to the Knodell system, fibrosis scores of ≤1 indicate mild HCV. Although the mean baseline fibrosis score was just over this threshold, the majority of patients (83%) were classified as having a fibrosis score less than F3, and therefore can be considered as having mild HCV [*NB*. The Knodell system has no F2 score; see the sections 'Biopsy classification systems' (p. 5) and 'Staging fibrosis' (p. 6) for more detail on biopsy classification systems]. The majority of patients were infected with genotype 1 (70%). Only 12% of patients treated with IFN achieved an SVR, compared with 18–23% of patients given various doses of PEG. Comparisons between PEG and IFN were statistically significant, but not for the 0.5 µg/kg group.

In summary, PEG monotherapy in trials containing predominantly mild HCV patients can result in SVRs of up to 30%, depending on PEG formulation and dose.

Studies reporting subgroups of mild HCV patients

Although trials that comprised less than 70% of patients with mild HCV were not included, such trials were considered if they reported outcomes according to baseline fibrosis stage scores. This enabled within-trial response rates to be gauged for patients with mild HCV in comparison with response rates for patients with moderate to severe disease. Eleven such studies were identified, three of which evaluated PEG and the remainder evaluating IFN. Below brief characteristics and results are reported for each study. Even though all are RCTs, caution is advised as, except for those of Poynard and colleagues[74] and Manns and colleagues,[17] they have not been subjected to full critical appraisal (full data extraction and critical appraisal of the trials by Poynard and colleagues and Manns and colleagues can be found in the previous assessment report;[11] this can be downloaded from www.ncchta.org). Furthermore, none of the trials were specifically designed to evaluate differences in response according to baseline fibrosis. Their results are presented here as context within which to interpret the results of the RCTs reported in the previous sections.

Pegylated interferon alfa studies

Poynard and colleagues (2002):[74] Meta-analysis of PEG 2b + ribavirin on fibrosis [incorporating Poynard and colleagues (2000)[75]]

Poynard and colleagues[74] conducted a meta-analysis to estimate the impact of antiviral treatment on liver fibrosis in patients who had achieved an SVR after antiviral treatment, and also those who did not. This supersedes their earlier meta-analysis of three RCTS of IFN and RBV (n = 1509 patients).[75] In the 2002 report, data from four similar pivotal RCTs that tested either IFN 2b or PEG 2b regimens in HCV were combined (one of which is Manns and colleagues' 2001 RCT of PEG 2b, reported below). These regimens could be either monotherapies or dual therapy combining RBV with IFN or PEG. The 'control' regimen was considered to be IFN 2b at a dose of 3 MU three times per week for 24 weeks. The results from the 10 included regimens were considered primarily for changes in liver fibrosis.

Data from 3010 treatment-naïve patients with pre- and post-treatment biopsies were pooled. Liver biopsies were scored using the METAVIR scoring system. Mean fibrosis stage varied between 1.3 and 1.5 depending on the study. This is slightly higher than the threshold for mild HCV in the METAVIR system (≤1). However, the proportion of patients with a METAVIR score of ≤1 varied between 68 and 78% across the studies. The majority of patients could therefore be considered as having mild HCV. This is endorsed by the authors, who report that at baseline 2243 patients had no significant fibrosis (75%), defined as METAVIR F0–F1.

Ten different treatment regimens were compared for the percentage of patients who improved by at least one fibrosis stage, remained stable or worsened by at least one stage. Regimens were also compared according to the fibrosis progression rates per year before and after treatment. The impact of different regimens on the percentage of patients with significant fibrosis at the second biopsy was also assessed adjusted by other risk factors in multivariate analyses. The authors report that there were no statistically significant differences between the 3010 patients with paired biopsies and the larger, randomised, population from which they were sampled.

Caution should be exercised in interpreting this report because only some of the comparisons are

randomised, within-trial comparisons. In addition, most of the included regimens (particularly those using PEG) were tested in only one or two trials. Finally, this analysis only considered trials using PEG or IFN 2b, hence the findings cannot necessarily be generalised to PEG 2a or IFN 2a.

A range of detailed results were presented. The key findings are as follows:

- 1094 (36%) were sustained virological responders, 1452 (48%) were virological non-responders and 464 virologically relapsed (16%).
- The SVR varied according to treatment regimen, ranging from 5 to 63%. Lowest rates were observed in the older interventions evaluated, such as IFN monotherapy (5–16%). Rates increased for different doses of PEG monotherapies (21–29%), followed by various regimens of IFN + RBV (34–51%), and reached their highest for various PEG + RBV doses (54–63%).
- Fibrosis stage improved in 20% of patients, stabilised in 65% and worsened in 15%, mostly in terms of a one-point change. Improvements were generally higher among PEG + RBV-treated patients and lower among those given IFN monotherapy.
- All regimens significantly reduced fibrosis progression rates relatively to pretreatment.
- There was significantly less worsening of fibrosis among patients who achieved SVR (7%) than among relapsers (17%) or non-responders (21%).
- Rates of fibrosis progression were lower after treatment in both virological responders and non-responders with no significant differences between different treatment regimens (but there was a significant difference between responders and non-responders).
- Six factors were independently associated with the absence of significant fibrosis after treatment: baseline fibrosis stage (F0/F1), SVR, age <40 years, body mass index <27 kg/m^2, no or mild baseline necroinflammatory activity (based primarily on necrosis) and viral load <3.5 million copies/ml.

Manns and colleagues (2001);[17] PEG 2b + RBV

Manns and colleagues[17] report an international multicentre RCT of PEG 2b + RBV compared with IFN + RBV (also included in Poynard's meta-analysis above). This was one of the pivotal registration trials included in the previous assessment report (the report contains a full data extraction and critical appraisal of this RCT and can be downloaded from www.ncchta.org). A total of 1530 patients were assigned to:

- IFN (3 MU three times per week) + RBV 1000–1200 mg/day for 48 weeks; *N* = 505
- PEG (1.5 μg/kg once per week) + RBV 800 mg/day for 48 weeks; the 'high PEG dose' group; *N* = 511
- PEG (1.5 μg/kg per week for 4 weeks, followed by 0.5 μg/kg per week for 48 weeks); the 'low PEG dose' group; *N* = 514.

Randomisation was stratified by genotype and absence or presence of cirrhosis. The journal publication states that biopsy samples were classified using the Knodell system, and reports the proportion of patients at baseline with bridging fibrosis/cirrhosis (fibrosis score 3 or 4). SVRs are stratified according to whether patients were classed as having no/minimal fibrosis (fibrosis scores 0–1) [note that the Knodell system has no fibrosis score of 2; see section 'Staging fibrosis' (p. 6) and Appendix 1 for further details], or whether they had bridging fibrosis/cirrhosis at baseline (and further stratified as to whether high or low ribavirin dose). The manufacturer also reports a subgroup analysis of the mild patients in this trial in their submission to NICE. It appears that classifications have been translated from Knodell into METAVIR. *Table 22* reports the proportions of patients falling into different fibrosis categories as reported in the manufacturer's submission and the journal publication.

The proportions of patients classed as mild according to the two classification systems appear to be generally similar. Roughly two-thirds of the randomised patients fell into this category. However, the figures in the journal article do not add up to the total number of patients in each study group. Data are missing for 102 of 1530 (7%) patients. This is probably due to missing pre- or postintervention biopsy data.

Table 23 presents the results, in terms of SVR, for all patients in the trial and for subgroups based on baseline fibrosis and ribavirin dose. The highest SVR (54%) was achieved in the high PEG dose group, followed jointly by the low PEG dose group (47%) and the IFN + RBV group (47%). The difference between the high PEG dose group and the IFN + RBV group was statistically significant. There was no significant difference between the low PEG dose group and the IFN + RBV group.

TABLE 22 *Baseline fibrosis scores for Manns and colleagues' PEG 2b trial*

	High PEG dose *N* = 511	Low PEG dose *N* = 514	IFN + RBV *N* = 505
Manufacturer's submission[76] (METAVIR)			
F0	8	0	0
F1	321	343	330
F0 + F1	329	343	330
Manns and colleagues[17] (Knodell)			
No/minimal fibrosis	333	345	336
Bridging fibrosis/cirrhosis	136	146	132

TABLE 23 *SVRs for all patients, and by baseline fibrosis (Manns and colleagues)*

	PEG 2b + RBV (high PEG dose)	PEG 2b + RBV (low PEG dose)	IFN + RBV
All patients	54% (274/511)[a]	47% (244/514)[b]	47% (235/505)
All patients, low RBV dose	50% (160/323)	41% (13/32)	27% (6/22)
All patients, high RBV dose	61% (114/188)	48% (231/482)	47% (229/483)
No/minimal fibrosis	57% (189/333)[c]	51% (175/345)[d]	49% (164/336)
No/minimal fibrosis, low RBV dose	54% (113/209)	40% (8/20)	22% (2/9)
No/minimal fibrosis, high RBV dose	61% (76/124)	51% (167/325)	50% (162/327)
Bridging fibrosis/cirrhosis,	44% (60/136)[e]	43% (63/146)[f]	41% (54/132)
Bridging fibrosis/cirrhosis, low RBV dose	39% (36/92)	42% (5/12)	25% (3/12)
Bridging fibrosis/cirrhosis, high RBV dose	55% (24/44)	43% (58/134)	43% (51/120)

[a] $p = 0.01$ for comparison with IFN + RBV.
[b] $p = 0.73$ for comparison with IFN + RBV.
[c] $p = 0.04$ for comparison with IFN + RBV.
[d] $p = 0.65$ for comparison with IFN + RBV.
[e] $p = 0.62$ for comparison with IFN + RBV.
[f] $p = 0.72$ for comparison with IFN + RBV.

SVRs were higher among the subgroup with no/minimal fibrosis, in the range 49–57%. Among patients with bridging fibrosis/cirrhosis, SVRs were lower, in the range 41–44%. On comparing SVRs for these subgroups between treatments, the only statistically significant difference was for the high PEG dose compared with IFN + RBV. SVRs also tended to be higher when a larger dose of ribavirin was used, reaching 61% for patients with no/minimal fibrosis and treated with the higher dose of PEG. However, caution is advised as no statistical significance values are reported for comparisons between patients with different disease severity.

Absence of bridging fibrosis/cirrhosis was significantly associated with SVR when tested in univariate logistic regression analysis ($p = 0.0001$). It was also an independent predictor of SVR when tested in multivariate regression.

Bruno and colleagues (2004):[123] PEG 2b + RBV in genotype 1 patients

Bruno and colleagues report an RCT of PEG 2b in combination with RBV for initial treatment of patients with genotype 1. Patients received 48 weeks of PEG + RBV (80–100 μg/day depending on body weight for 8 weeks, followed by 50 μg/day for the next 40 weeks) ($n = 163$), or IFN 6 MU on alternate days ($n = 148$). Both regimens contained ribavirin 1000–1200 mg/day. The mean Ishak fibrosis score was 2.61–2.62 across the two study groups. A total of 201 patients (65%) were classified as having mild HCV at baseline, based on an Ishak fibrosis score of either 1 or 2 (no patients with zero score are reported).

The SVR was 41% (PEG + RBV) vs 29.7% (IFN + RBV), $p = 0.037$. SVRs are also reported by each of the Ishak stages for the sample as a whole (*Table 24*). As the table shows, the highest SVRs were experienced by patients in stages 1 and 2.

TABLE 24 *SVR by baseline fibrosis (Bruno and colleagues)*

Ishak fibrosis stage	SVR: *n/N* (%)[a]
1	31/55 (56)
2	61/146 (42)
3	9/44 (20)
4	5/23 (22)
5	3/15 (20)
6	2/28 (7)

[a] $p = 0.001$.

Although the authors do not tabulate SVRs by baseline fibrosis stage for the respective study groups, they do provide a bar chart of SVRs by baseline stage for the PEG + RBV group. In the text they report that 19 of 31 patients (61.3%) with stage one fibrosis had an SVR, and that only one of 14 patients (7.1%) with stage 6 fibrosis (cirrhosis) had an SVR. The SVRs for the intermediate stages were estimated by reading off the graph, as follows: stage 2 (58%), stage 3 (31%), stage 4 (21%) and stage 5 (19%). Multivariate analysis also confirmed mild baseline fibrosis as an independent predictor of SVR.

(Non-pegylated) interferon alfa studies

August-Jorg and colleagues (2003):[77] Re-treatment with IFN 2b and RBV in IFN monotherapy relapsers

August-Jorg and colleagues[77] report a small pilot RCT of 24 versus 48 weeks of IFN + RBV in patients who had relapsed following previous IFN monotherapy. Of the 19 patients assigned to the 24-week treatment, nine (50%) were classed as having 'none/mild' fibrosis at baseline, with the remaining nine classed as 'moderate/severe/cirrhosis'. Of the 18 patients receiving 48 weeks of treatment, the proportions were eight (44%) and nine (50%), respectively. Histology was classified using the METAVIR system. Sustained responses (SRs) were 10/19 (53%) in the 24-week group and 13/18 (72%) in the 48-week group. For the 24-week treatment group the SR was higher for the moderate to severe fibrosis group [7/10 (70%)], compared with the none/mild fibrosis group [3/9, (33%)]. This pattern was reversed in the 48-week treatment group, where the SR in the none/mild fibrosis group was higher than that in the moderate to severe fibrosis group [10/12 (83%) vs 2/5 (40%)]. However, caution is advised as these are relatively small numbers of patients, and statistical significance values are not reported.

Berg and colleagues (2000):[78] Induction treatment with IFN 2a and RBV followed by interferon alone

Berg and colleagues[78] report results of an RCT evaluating induction therapy with IFN + RBV followed by IFN monotherapy in previously untreated patients. A total of 85 patients recruited from university clinics in Germany were randomised to the following treatment groups:

- IFN 6 MU three times per week + RBV for 12 weeks ($n = 93$)
- IFN 6 MU three times per week for 12 weeks ($n = 92$)

Patients achieving a 12-week viral response in both groups continued for a further 40 weeks with IFN monotherapy at a dose of 3 MU three times per week.

All patients received a liver biopsy prior to therapy, with findings classified according to what appears to be the METAVIR system (the authors cite papers by Hytiroglou and colleagues[79] and Desmet and colleagues[80] in relation to histological classification). The mean fibrosis stage at baseline in both treatment groups was 1.5. The proportion of patients classed as having fibrosis with numerous septa (stage 3) was 20 (11%), and the number with cirrhosis (stage 4) was 2 (1%).

A 12-week response was achieved by 61/93 (66%) of patients in the IFN + RBV group, compared with

TABLE 25 *SVR by baseline fibrosis (Berg and colleagues)*

	IFN + RBV			IFN monotherapy		
	Non-response/relapse	SVR	*p*-Value	Non-response/relapse	SVR	*p*-Value
Fibrosis stage[a]	1.5 (± 0.12)	1.3 (± 0.18)	0.42	1.5 (± 0.1)	0.9 (±0.2)	0.007
Stage ≤ 1[b]	42/59 (71)	17/59 (29)	0.25	45/59 (76)	14/59 (24)	0.027
Stage > 1[b]	27/34 (79)	7/34 (21)		31/33 (94)	2/33 (6)	

[a] Mean ± Standard error of the mean (SEM).
[b] *n/N* (%).

TABLE 26 *SVR by baseline fibrosis (de Ledinghen and colleagues)*

	Total: *n* (%)	Group A: *n* (%)	Group B: *n* (%)	Group C: *n* (%)
Minimal or no fibrosis	186 (59.8)	4/57 (7.0)	18/69 (26.1)	18/60 (30)
Cirrhosis or bridging fibrosis	125 (40.2)	3/45 (6.7)	5/35 (14.3)	9/45 (20)

44/92 (48%) in the IFN monotherapy group ($p = 0.015$). An SVR was achieved by 24/93 (26%) in the IFN + RBV group compared with 16/92 (17%) in the IFN group, although the difference was not significant ($p = 0.10$). *Table 25* presents the results of the subgroup analyses by mean baseline fibrosis stage and proportion of patients with fibrosis scores ≤1 or >1 (the threshold for defining mild HCV).

A lower mean fibrosis stage was associated with SVR in both treatment groups, although the difference was significant only for IFN monotherapy. In both treatment groups a higher proportion of patients who achieved an SVR were classed as fibrosis stage ≤1. However, fibrosis stage (≤1 or >1) was associated with SVR only in the IFN monotherapy group.

de Ledinghen and colleagues (2002a):[81] Daily or three times per week IFN 2b plus RBV in patients not responding to previous INF

The aim of this study was to compare two regimens of IFN + RBV with IFN monotherapy in patients who had failed a previous course of IFN monotherapy. Patients were randomised to:

- 6 MU IFN three times per week for 24 weeks, followed by 3 MU three times per week for 24 weeks (group A)
- 6MU IFN three times per week + RBV for 24 weeks, followed by 3 MU three times per week + RBV 24 weeks (group B)
- 3MU IFN daily + RBV for 24 weeks, followed by 3 MU three times per week + RBV for 24 weeks (group C).

Of the 398 patients randomised, 376 received treatment (group A = 120; group B = 129, group C = 127). Baseline METAVIR scores are reported for 311 (82%) of those treated. The proportion of patients with METAVIR fibrosis scores ≤1 was 96/311 (33%). The majority of patients were classified as METAVIR F2/F3. The proportion of cirrhotic patients (METAVIR F4) was 56 (18%).

SVRs were achieved by seven (6%), 27 (21%) and 33 (26%) of patients in groups A, B, and C, respectively. Differences between groups B and A and groups C and A were statistically significant.

SVRs were reported for subgroups of patients, 'cirrhosis or bridging fibrosis' ($n = 125$) and 'minimal or no fibrosis' at baseline ($n = 186$). Their definition of the latter includes patients with METAVIR scores ≤2, which is one stage higher than the threshold used in this report for defining mild HCV [see the section 'Patients' (p. 18)]. *Table 26* presents the results.

In groups B and C, SVRs were around 10% higher for the 'minimal or no fibrosis' subgroup than the 'cirrhosis or bridging fibrosis' subgroup. However, for Group A the difference was marginal. No significance values are presented between treatment groups or patient subgroups. Logistic regression was performed to assess the association between a number of factors and SVR. In the univariate analysis METAVIR fibrosis score F0, F1 or F2 versus F3 or F4 was not significantly related to SVR ($p = 0.06$). However, it was significant in the multivariate analysis ($p = 0.001$).

In summary, this study shows that SVRs were generally higher for mild HCV patients treated with IFN + RBV for 24 weeks compared with those with moderate to severe HCV. However, the subgroup of patients with minimal or no fibrosis included a substantial proportion of patients with METAVIR fibrosis score 2, considered to be in the moderate category of disease severity, according to the definition of mild HCV used in this report.

de Ledinghen and colleagues (2002b):[82] Daily or three times per week IFN 2b plus RBV in previously untreated patients

The purpose of this second trial by De Ledinghen and colleagues[82] was to compare IFN monotherapy with the standard regimen of IFN given three times per week in combination with RBV, or an induction dose of daily IFN in combination with RBV in previously untreated patients:

- IFN 3 MU three times per week for 48 weeks (group A)
- IFN 3 MU three times per week + RBV daily for 48 weeks (group B)
- IFN 3 MU daily + RBV daily for 12 weeks followed by 3 MU three times per week for 24 weeks (group C).

TABLE 27 *SVR by baseline fibrosis (de Ledinghen and colleagues)*

	Total: *n* (%)	Group A: *n* (%)	Group B: *n* (%)	Group C: *n* (%)
Minimal or no fibrosis	230 (72.6)	18/64 (28.1)	48/83 (57.8)	39/83 (47.0)
Cirrhosis or bridging fibrosis	87 (27.4)	5/27 (18.5)	11/31 (35.5)	14/29 (48.3)

Of the 338 patients randomised, 321 underwent treatment (group A = 92, group B = 114, group C = 115). The proportion of patients with METAVIR fibrosis scores ≤1 was 107 (33%). The majority of patients scored between METAVIR 2 and 3, with a small proportion (<10%) classed as cirrhotic.

SVRs were achieved by 23 (25%), 59 (52%) and 53 (46%) of patients in groups A, B and C respectively. Differences between groups B and A and groups C and A were statistically significant. No statistically significant difference was observed between groups B and C. SVRs were reported for subgroups of patients, 'cirrhosis or bridging fibrosis' (n = 87) and 'minimal or no fibrosis' at baseline (n = 230). Their definition of the latter includes patients with METAVIR scores ≤2, which is one stage higher than the threshold used in this report for defining mild HCV [see the section 'Patients' (p. 18)]. *Table 27* presents the results.

For groups A and B, SVRs were higher in the 'minimal or no fibrosis subgroup' than the 'cirrhosis or bridging fibrosis subgroup'. No statistical significance values are presented for these comparisons. In group C, SVRs were similar. METAVIR fibrosis stage F1/F2 was not a significant predictor of virological response when tested in a univariate logistic regression analysis.

In summary, this study shows that SVR was more common in patients with less fibrosis at baseline. However, the subgroup of patients with minimal or no fibrosis included a substantial proportion of patients with METAVIR fibrosis score 2 (approximately 38%), considered to be in the moderate category of disease severity, according to the definition of mild HCV used in this report. Furthermore, METAVIR fibrosis score was not a significant predictor of viral response.

Di Bisceglie and colleagues (2001):[124] IFN 2b and RBV in the retreatment of non-responders to IFN
Di Bisceglie and colleagues recruited patients who had not responded to a previous course of interferon monotherapy from the liver clinic of Saint Louis University in the USA. A total of 124 patients were randomised to receive IFN + RBV for either 24 or 48 weeks. All patients received a biopsy prior to treatment, with samples classified according to the Scheuer system [see the section 'Staging fibrosis' (p. 6)]. The proportion of patients with a baseline fibrosis score of 1 was 24 (19%), compared with 32 (26%) for stage 2, 41 (33%) for stage 3 and 27 (22%) for stage 4. A score of 1 or less indicates mild HCV on this system.

In the 24-week group the SVR was 17/63 (27%), whereas in the 48-week group it was 22/61 (36%). SVRs, pooled for the 24- and 48-week treatment groups, are presented according to baseline fibrosis. The SVR for fibrosis stage 1 patients was 6/38 (16%), compared with 11/38 (29%), 15/38 (39%) and 6/38 (16%) for stages 2, 3 and 4, respectively. In this study, therefore, the highest SVRs were achieved by patients in the moderate fibrosis category. Caution is advised, however, as patient numbers are relatively small and the difference between responders and non-responders in the fibrosis subgroups was not significant. Significance values between the fibrosis subgroups themselves are not reported.

Getachew and colleagues (2004):[83] IFN 2b and RBV in previously treated/untreated veterans
Getachew and colleagues[83] report a small RCT of previously treated and untreated patients recruited from the Dallas Veterans Affairs Medical Center, USA. The aim of the trial was to evaluate the effectiveness of high dose induction therapy with IFN in combination with RBV, compared with standard dose combination therapy.

Patients were randomly assigned to the following groups:

- IFN daily for 4 weeks (5 MU), followed by IFN (3 MU) three times per week for 44 weeks, plus RBV for the entire period (high induction dose group)
- IFN (3 MU) three times per week, plus daily RBV for 48 weeks (standard dose group).

Patients with genotypes 2 and 3 were treated for only 24 weeks. The Knodell system was used to classify biopsy samples. At baseline the majority of patients (31/68%) had bridging fibrosis or cirrhosis

TABLE 28 *SVR by baseline fibrosis and genotype (Getachew and colleagues)*

Subgroup	Total: *n*/*N* (%)	High induction dose: *n*/*N* (%)	Low dose: *n*/*N* (%)
F stage 0–1	3/10 (30)	1/3 (33)	3/7 (43)
F stage 3–4	10/31 (32)[a]	5/17 (29.4)	4/14 (28.6)
SVR genotype 1	7/34 (20)	3/17 (17.6)	4/17 (23.5)
F stage 0–1	1/7 (14.3)	0/2 (0)	1/5 (20)
F stage 3–4	6/24 (25)[b]	3/14 (21)	3/10 (30)
SVR genotype 2A/2B, 3A/3B	7/11 (64)	4/5 (80)	3/6 (50)
F stage 0–1	3/3 (100)	1/1 (100)	2/2 (100)
F stage 3–4	3/7 (42.8)[c]	2/3 (67)	1/4 (25)

[a] $p = 1.00$ (stage 3–4 vs stage 0–1)
[b] $p = 1.00$ (stage 3–4 vs stage 0–1)
[c] $p = 0.2$ (stage 3–4 vs stage 0–1)

(stages 3–4), with the remaining patients either having no or minimal fibrosis (stages 0–1) (10/22%) or unclassified (4/8%). This trial, therefore, had a high proportion of patients with advanced HCV-related liver disease.

SVRs were similar between the two treatment groups. In the high induction dose group the rate was 7/22 (31.8%), compared with 7/23 (30.4%) in the standard dose group. Subgroup analyses explored SVRs according to baseline fibrosis stage and genotype. The latter was further stratified by fibrosis stage. *Table 28* presents the results.

For the sample as a whole there was no significant difference in SVR between fibrosis stages 0–1 and 3–4 ($p = 1.00$). Within the genotypes, and for the sample as a whole, there were no significant differences between fibrosis stages. The authors suggest that the higher SVR among genotype 1 patients with stage 3–4 fibrosis/cirrhosis was due to small sample size, rather than to any actual difference in response. This study, therefore, shows that there were no significant differences in response between patients with mild and moderate to severe HCV. The study is likely to be underpowered to be able to detect significant differences.

Mangia and colleagues (2002):[84] High-versus low-dose IFN 2b plus RBV in previously untreated patients

The aim of this open-label RCT by Mangia and colleagues[84] was to compare a high dose of IFN (5 MU) to the lower, standard dose (3 MU) in patients recruited from seven community hospitals in the south of Italy. Both doses of IFN were administered in combination with RBV for 12 months. A total of 298 patients were treated, 148 in the 5-MU group and 150 in the 3-MU group. The Scheuer system was used for classifying biopsy samples. At baseline 121 (41%) of the sample were classified as having a fibrosis score of ≤1 (indicating mild HCV). SVRs were 71/148 (48%) in the 5-MU group, and 61/150 (40%) in the 3-MU group. However, differences were not statistically significant ($p = 0.25$). The effect of baseline histology was explored in univariate analysis. For stage 0–1 patients there were 67 sustained responders (50.7%) compared with 54 (32.5%) non-responders. For stages 2–3 the proportions were 65 (49%), and 112 (67.4%), respectively. The proportion of sustained responders with mild HCV was similar to those with moderate HCV. Differences between sustained responders and non-responders were statistically significant ($p = 0.002$).

Poynard and colleagues (2000):[85] Pooled analysis of two pivotal IFN 2b and RBV RCTs

Poynard and colleagues[85] present a pooled analysis of two multicentre international RCTs of IFN + RBV in comparison with IFN monotherapy in previously untreated patients (by Poynard and colleagues[18] and McHutchison and colleagues;[86] full data extraction and critical appraisal of these trials can be found in the earlier assessment report,[87] which can be downloaded from www.ncchta.org). The purpose of pooling them was to increase the power of the analysis to ascertain, amongst other things, which factors were associated with SVR.

The total number of patients analysed was 1744, all of whom were treatment naïve. The METAVIR system was used to classify histological status, although the baseline histological profile of the sample is not reported. Four treatment groups are included, two evaluating IFN + RBV (48 and 24 weeks) and two evaluating IFN + placebo

TABLE 29 *SVR by baseline fibrosis (Poynard and colleagues)*

Fibrosis stage	IFN + RBV 48 weeks: *n/N* (%)	IFN + RBV 24 weeks: *n/N* (%)	IFN 48 weeks: *n/N* (%)	IFN 24 weeks: *n/N* (%)
No or portal fibrosis (0–1)	158/368 (43)	129/362 (36)	63/351 (18)	7/154 (5)
Septal fibrosis or more (2–4)	36/101 (36)	27/118 (23)	14/119 (12)	3/65 (5)

(48 and 24 weeks); SVRs for the four groups were 41% (205/505), 33% (166 of 505), 16% (82 of 503) and 6% (13 of 231), respectively. Significant differences were found between all groups.

Table 29 shows the SVRs for the subgroup of patients with 'no or portal fibrosis' (stage 0 to 1) or 'septal fibrosis or more' (stage 2–4).

In general, SVRs were higher in the 'no or portal fibrosis' group. No or portal fibrosis was also a significant independent predictor of treatment response in logistic regression analysis.

Summary

- The aim of this section was to review briefly RCTs/meta-analyses which reported within-trial SVRs according to subgroups of patients with mild and moderate to severe HCV.
- Eleven studies were found ranging from international multicentre RCTs to small-scale pilot RCTs. Three evaluated PEG and eight evaluated IFN. The majority of reports evaluated PEG 2b/IFN 2b. Doses and regimens varied considerably.
- Around half of the studies included previously untreated patients. The other half included patients who were retreated following non-response or relapse to previous treatment.
- In general, higher SVRs were observed for patients classified as having mild HCV at baseline, compared with those classified as moderate to severe HCV (seven studies). However, this was statistically significant in only one study, with the remaining studies not reporting any significance values. Another study reported no statistically significant difference in SVRs between mild and moderate to severe fibrosis.
- In five studies no or minimal fibrosis was significantly and independently associated with SVR, as assessed in multivariate logistic regression analyses.
- In a meta-analysis of RCTs, baseline fibrosis stage (F0/F1) was associated with absence of significant fibrosis after treatment.

Chapter 5
Economic analysis

Introduction

The aim of this section is to assess the cost-effectiveness of treating adults with mild chronic hepatitis C in England and Wales with interferon (pegylated or non-pegylated) compared with the existing strategy of only treating once the disease has progressed to moderate or severe chronic hepatitis C or best supportive care. The economic analysis comprises:

- a systematic review of the literature on the cost-effectiveness of interferon-based treatments in adults with mild chronic hepatitis C (the next section)
- a review of the manufacturers' submissions (cost-effectiveness section) to NICE [the subsequent section (p. 62)].
- presentation of the economic model and cost-effectiveness evaluation (Chapter 6).

Systematic review of the literature

Methods for the systematic review

A systematic literature search was undertaken to identify economic evaluations reporting interferon-based treatment for adults with mild chronic hepatitis C compared with delaying treatment until the disease has progressed to moderate or severe chronic hepatitis C or compared with best supportive care. The details of databases searched and search strategy are documented in Appendix 4. The manufacturers' submissions to NICE were reviewed for additional studies.

Titles and abstracts of studies identified by the search strategy were assessed for potential eligibility by a health economist. Economic evaluations were eligible for inclusion if they were full economic evaluations reporting on the cost-effectiveness of (pegylated or non-pegylated) interferon treatment for adults with mild chronic hepatitis C compared with treatment once the disease has progressed to moderate or severe chronic hepatitis C or compared with best supportive care.

Results of the systematic review: cost-effectiveness

A total of 316 publications relating to cost-effectiveness of treatment for adults with chronic hepatitis C were identified through the search strategies. Of these:

- 65 were identified as full economic evaluations. No systematic reviews of the cost-effectiveness of treating mild chronic hepatitis C were identified by the search.
- 37 of the full economic evaluations were initially excluded as they were not concerned with antiviral treatment of chronic hepatitis C or were evaluations in non-adult populations.
- The remaining 29 economic evaluations of antiviral treatment of chronic hepatitis C were decision analyses using data on treatment effects derived from clinical trials, with the majority adopting a common natural history model.[88]
- Only seven[12,88–93] were concerned with interferon treatment for patients with mild chronic hepatitis C. One of these[89] was excluded from this review as it was solely concerned with the incremental cost-effectiveness of dual therapy compared with monotherapy and did not evaluate interferon-based treatment compared with no treatment or delayed treatment. While the remaining 22 evaluations included patients with mild disease in the cohorts modelled, only one reported separate analyses by stage of disease.[94] This evaluation did not indicate the criteria for defining mild disease or the source of the effectiveness data used to model treatment for patients with mild disease and is not reviewed here.
- Only two of the six published evaluations for interferon treatment for patients with mild chronic hepatitis C in the review included PEG as an intervention.

Table 30 provides a summary of the characteristics and base case finding for the six published economic evaluations reporting the cost-effectiveness of interferon-based treatment for mild chronic hepatitis C (see also Appendices 18–23 for full data extraction and critical appraisal

TABLE 30 *Characteristics of economic evaluations of interferon treatment for mild chronic hepatitis C*

	Bennett et *al.*[88]	**Davis et *al.*[90]**	**Wong and Koff[92]**	**Grieve and Roberts[93]**	**Salomon et *al.*[91]**	**Grieve et *al.*[12]**
Publication year	1997	1998	2000	2002	2003	2005
Country	USA	USA	USA	Europe	USA	UK
Study type	Cost-effectiveness analysis (CEA) model	Cost-utility analysis (CUA) model	CUA model	CUA model	CUA model	CUA model
Study population	Mild chronic HCV	Mild chronic HCV	Mild chronic HCV with elevated ALTs	Mild chronic HCV	Mild with elevated ALTs	Mild chronic HCV
Intervention(s)	IFN 2b monotherapy versus no antiviral treatment	IFN 2b monotherapy for varying durations versus no antiviral treatment	Four strategies: 1. no antiviral treatment 2. early treatment 3. watchful waiting with treatment once cirrhotic 4. watchful waiting with treatment once moderate. Treat with IFN 2b dual therapy	Immediate treatment with combination versus treatment on development of moderate chronic HCV (current UK guideline)	Five strategies: 1. No antiviral treatment 2. IFN 2b monotherapy 3. PEG 2b monotherapy 4. IFN 2b dual therapy 5. PEG 2b dual therapy	Immediate treatment with IFN 2b dual therapy versus treatment on development of moderate chronic HCV (current UK guideline) Assume same response for mild and moderate patients
Treatment effect modelled	SVR (persistently normal serum ALT level for at least 6 months after completion of treatment). Same SVR (27%) applied to mild and moderate patients based on pooled results of five clinical trials[95–99]	SVR (persistently normal serum ALT level for at least 6 months after completion of treatment). SVR of 36.4% for 18–24 months and 15.3% for 6-month course were applied based on pooled results of two clinical trials[99,100]	SVR (not defined). SVR of 71.6 and 36.7% for women with genotype 2/3 and non-2/3, respectively. 62.5% and 27.7% for men with genotype 2/3 and non-2/3, respectively. Based on pooled results of two clinical trials.[18,86] Same SVR for early and delayed treatment	SVR (not stated – definition for trial was absence of HCV RNA in the serum at 24 weeks post-treatment cessation[65]). SVR or 43% based on one clinical trial[18] assuming 50:50 ratio of genotype 1 and genotype non-1 patients. Assume same response for mild and moderate patients	SVR (undetectable HCV RNA in the serum for at least 6 months after treatment cessation). SVR of 31% (6%) for IFN dual (mono) and 42% (15%) for PEG dual (mono) therapy in genotype 1. SVR of 67% (26%) for IFN dual (mono) and 79% (47%) for PEG dual (mono) therapy in genotype non-1. Based on pooled results of five clinical trials[17,18,73,86,101]	SVR (not stated – definition for trial was absence of HCV RNA in the serum at 24 weeks post-treatment cessation[65]). SVR of 33% (18% genotype 1 and 49% genotype non-1) based on one clinical trial[65] for IFN. SVR for PEG (24% genotype 1 and 55% genotype non-1), based on OR for SVR for PEG compared with IFN from one clinical trial[17]

continued

TABLE 30 *Characteristics of economic evaluations of interferon treatment for mild chronic hepatitis C (cont'd)*

	Bennett et *al.*[88]	Davis et *al.*[90]	Wong and Koff[92]	Grieve and Roberts[93]	Salomon et *al.*[91]	Grieve et *al.*[12]
Currency base		1995 US$	1998 US$	2001 Euros	US$	2002–03 UK£. Report 2002–03 US$ for comparison
Base case results	35-year-old with mild chronic HCV gain 0.26 life years (discounted at 5%) with incremental cost of $490 (discounted at 5%) for IFN 2b treatment compared with standard care. Discounted incremental QALYs not reported	35-year-old with mild chronic HCV gains 0.98 QALYs from 6 months and 2.26 QALYs from 18–24 months of treatment (discounted at 3%) with incremental lifetime cost of $609 and $1732, respectively (discounted at 3%) for IFN 2b treatment compared with standard care. ICERs were $621 and $766, respectively	Cohort with mean age of 40 years, over 20 years strategy 4 reduces cirrhosis to 18% compared with 28% with no treatment and avoids treatment in 50% of cohort compared with strategy 2. Incremental QALYs for strategy 2 and strategy 4 vs no treatment are 1.1 and 0.6, respectively. Incremental costs are $7000 and $6720, respectively	Cohort of 1000 patients with mean age of 40 years would experience 55 fewer deaths with early treatment. The gain in life expectancy is 1.2 years and 1.8 QALYs compared with delayed treatment. Incremental costs of early treatment were €14,882. ICERs quoted were €12,089 per life-year gained and €8490 per QALY gained	Probability of developing cirrhosis over 30 years ranged from 13 to 46% in men and 1 to 29% in women. Substantial range in ICERs for dual therapy with PEG ($26,000–64,000 for genotype 1 and $10,000–28,000 for genotype non-1 in men; $32,000–90,000 for genotype 1 and $12,000–42,000 for genotype non-1 in women). Benefits largely depend on improved quality of life, not survival	Genotype non-1 patients gain 0.61 QALYs with early treatment over delayed treatment. Incremental lifetime cost of £2300 with IFN. £3733/QALY for IFN 2b dual therapy (£28,754 for PEG). Lower QALY gain for genotype 1 (0.18) for early treatment. Incremental lifetime cost of £4000. ICERs are £23,029/QALY for IFN 2b dual therapy (£36,440 for PEG)[a]

[a] These results differ from those in the on-line publication[12] and have been supplied by the lead author (Grieve R, London School of Hygiene and Tropical Medicine, London University: personal communication, 2005).

of each study). The studies are either US or European/UK based (one of these[12] is the cost-effectiveness analysis of the UK Mild HCV Trial, which is included in the section 'Assessment of effectiveness' (p. 23)], although the clinical literature used to derive estimates of the effectiveness of interferon-based treatment for mild chronic hepatitis C covers a wide range of countries and institutional settings. All studies that compared antiviral treatment with best supportive care indicate that it is effective in terms of improved life expectancy and quality-adjusted life expectancy compared with no antiviral treatment. Those studies which have compared the effects of early versus delayed treatment (i.e. watchful waiting) have generally shown that early intervention is cost-effective for genotype non-1 patients. Early treatment is less likely to be cost-effective for genotype 1 patients, due to the lower SVRs observed for this subgroup, and for whom the recommendation from these analyses has been to wait until moderate disease develops before starting treatment.

Estimation of outcomes within economic evaluations

The economic evaluations used state transition (Markov) models to simulate disease progression in their estimation of the cost-effectiveness of interferon-based treatment for mild chronic hepatitis C.

The state transition diagrams presented in each of these evaluations are broadly similar. They assume that, in the absence of treatment, patients with mild chronic hepatitis C will either remain in that state or will progress to moderate disease. Among those whose disease progresses, a proportion will develop cirrhosis, which may progress further to decompensated disease. Those who develop decompensated cirrhosis, or who develop hepatocellular carcinoma as a result of their HCV infection, face mortality risks greater than in the general population. The models all assume that there are no excess mortality risks for all other health states and that individuals in those states face the all-cause general population mortality risk.

Each of the models adopted for these evaluations allows the possibility of patients with progressive liver disease undergoing liver transplantation. Bennett and colleagues[88] specified in their state transition model that transitions were allowed from the decompensated cirrhosis health states (ascites, variceal haemorrhage and hepatic encephalopathy) to liver transplantation but not from hepatocellular carcinoma. The majority of included papers followed this same assumption, either by directly adopting the same decision model[90,92] or by citing this assumption within their tables of transition probabilities.[91,93]

Table 31 presents an outline of the approaches used to model disease progression and treatment effects in cost-effectiveness models for antiviral treatment in mild chronic hepatitis C. *Table 32* reports the transition probabilities adopted in the economic evaluations reviewed here, while *Table 33* (see later) presents the health state utilities used in their models. All the evaluations modelled disease progression for a specified cohort of patients starting with mild chronic hepatitis C. Definitions of mild disease vary between the included studies. Although each study based the definition of mild disease on histological measures, they varied as to whether they used a purely fibrosis-based measure[91] or a combination of fibrosis and inflammation scores.[12,88,90,92,93] Moreover, different scoring systems were adopted for defining severity of liver disease. However, the fibrosis-based definitions used for mild disease under each of these scoring systems in the included studies are consistent with those indicated in the mapping presented by Kleiner,[15] reproduced in this report in *Table 1*.

There are variations between studies in the methods adopted for estimating early disease transition probabilities. Bennett and colleagues[88] estimated transitions from mild to moderate disease and from moderate disease to cirrhosis from three observational studies of patients with non-A and non-B chronic hepatitis, which included serial liver biopsies.[102–104] The paper reports that these studies included 47 patients with mild disease, with a mean follow-up of 8.9 years, and 79 with moderate disease, with a mean follow-up of 6.6 years, but does not state how the quoted transition probabilities were derived. These estimates were subsequently adopted by Davis and colleagues[90] and Wong and Koff.[92]

Salomon and colleagues[91] extracted data on fibrosis progression from intervention trials that included serial liver biopsies and cross-sectional studies that included fibrosis stage related to duration of infection.[105–108] These studies were used to estimate ranges for age- and sex-specific fibrosis progression rates to be used in simulation models. Predicted outcomes from the simulations were compared with epidemiological data on

TABLE 31 *Model structure/assumptions for cost-effectiveness models for antiviral treatment of mild chronic HCV*

	Bennett et al.[88]	Davis et al.[90]	Wong and Koff[92]	Grieve and Roberts[93]	Salomon et al.[91]	Grieve et al.[12]
New model	Yes	No – adapted from Bennett and colleagues[88]	No – adapted from Bennett and colleagues[88]	No – adapted from Dusheiko and Roberts[110]	No – adapted from Bennett and colleagues,[88] but using METAVIR scoring system to define fibrosis stages	No – adapted from Grieve and Roberts[93]
Number of states	11 Remission/SVR Mild chronic HCV Moderate chronic HCV Chronic HCV with cirrhosis Ascites Refractory ascites Variceal bleed HE HCC Liver transplant Death	11 Remission/SVR Mild chronic HCV Moderate chronic HCV Chronic HCV with cirrhosis Ascites Refractory ascites Variceal bleed HE HCC Liver transplant Death	11 Remission/SVR Mild chronic HCV Moderate chronic HCV Chronic HCV with cirrhosis Ascites Refractory ascites Variceal bleed HE HCC Liver transplant Death	8 Remission/SVR Mild chronic HCV Moderate chronic HCV Cirrhosis Decompensated cirrhosis HCC Liver transplant Death	12 Remission/SVR F0[c] F1 F2 F3 F4 Ascites Variceal bleed HE HCC Liver transplant Death	8 Remission/SVR Mild chronic HCV Moderate chronic HCV Cirrhosis Decompensated cirrhosis HCC Liver transplant Death
Chronic HCV severity	Mild: PPI ≤ 1 and F ≤ 1[a] Moderate: F = 3 or (F ≤ 1 and (PPI ≥ 3 and PPI ≤ 10) Cirrhosis: F = 4	Mild: PPI ≤ 1 and F ≤ 1[a]	Mild: raised ALT and PPI ≤ 1	Mild: NI ≤ 3, F ≤ 2[b], serum positive for HCV, with normal or raised ALT	Mild: F0[c] serum positive for HCV, with raised ALT	Mild: NI ≤ 3, F ≤ 2[b], serum positive for HCV, with normal or raised ALT
Cycle length	1 year	1 year	1 year	1 year	1 year	1 year
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime	Lifetime	Lifetime
Baseline cohort	35 years old with mild chronic HCV	35 years old with mild chronic HCV	40 years old, 35% female, 32% genotype 2/3	40 years old with mild chronic HCV	40 years old (% female and % by genotype not reported) with raised ALT and no fibrosis	40 years old with mild chronic HCV

continued

TABLE 31 *Model structure/assumptions for cost-effectiveness models for antiviral treatment of mild chronic HCV (cont'd)*

	Bennett et *al.*[88]	**Davis et *al.*[90]**	**Wong and Koff[92]**	**Grieve and Roberts[93]**	**Salomon et *al.*[91]**	**Grieve et *al.*[12]**
Genotype	No account taken of genotype	No account taken of genotype	SVRs vary by genotype and sex. Outcomes (life-years and QALYs) reported by genotype, but not cost-effectiveness	SVRs vary by genotype. Results not reported by genotype	SVRs vary by genotype. Cost-effectiveness results reported by genotype and sex	SVRs vary by genotype. Cost-effectiveness results reported by genotype

HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; NI, necro-inflammation score (Ishak); PPI, peri-portal inflammation score (Knodell).
[a] F, fibrosis score (Knodell).
[b] F, fibrosis score (Ishak).
[c] F0, F1, F2, F3, F4, stages in METAVIR fibrosis scoring system (see Appendix I for definitions of fibrosis stages).

TABLE 32 *Transition probabilities used in published economic evaluations*

Health state							
From	**To**	**Bennett et *al.*,[88] Davies et *al.*,[90] Wong and Koff[92]**	**Salomon et *al.*[91]**			**Grieve and Roberts[93]**	**Grieve et *al.*[12]**
Mild chronic HCV	Remission	0.002		0.012		0.000	0.000
Mild chronic HCV	Moderate chronic HCV	0.041	Age (years)	Male	Female[a]	0.060	0.025
			40–49	0.054	0.028		
			50–59	0.125	0.065		
Moderate chronic HCV	Compensated cirrhosis	0.073	60–69	0.221	0.114	0.060	0.037
			70–79	0.301	0.154		
			≥80	0.301	0.210		
Moderate disease	HCC	0.001		0.000		0.000	0.000
Compensated cirrhosis	Decompensated cirrhosis	Asc 0.025 VH 0.011 HE 0.004		0.040		0.040	0.039
Compensated cirrhosis	HCC	0.015		0.021		0.000	0.014
Decompensated cirrhosis	HCC	0.000		0.000		0.010	0.014
Decompensated cirrhosis	Liver transplant	0.031		0.031		0.030	0.020
HCC	Liver transplant	0.000		0.000		0.000	0.00
Decompensated cirrhosis	Decompensated cirrhosis	Asc → R Asc 0.067		NA		NA	NA
Decompensated cirrhosis	Death	Asc 0.110 R Asc 0.330 VH Yr 1 = 0.400 Yr 2 = 0.130 HE Yr 1 = 0.680 Yr 2 = 0.400		0.306		NR	0.130
HCC	Death	0.860		0.433		NR	0.43
Liver transplant	Die	Yr 1 = 0.210 Yr 2 = 0.057				NR	Yr 1 = 0.150 Yr 2 = 0.030

Asc, ascites; NA , not applicable; NR, not reported; R Asc, refractory ascites; VH, variceal haemorrhage.
[a] The reported progression probabilities are for progression through METAVIR fibrosis stages. The mild and moderate disease health states each comprise two METAVIR stages (see *Table 1*); these values for progression between fibrosis stages are not directly comparable with transition probabilities for movement between adjacent health states.

prevalence of HCV and mortality from hepatocellular carcinoma (HCC) in the USA. A subset of parameter values, which were selected on the basis of goodness of fit,[109] were used in the economic model. The fibrosis progression rates adopted for the economic model increase with age, in contrast to those adopted in the previous evaluations, in which progression rates were constant with respect to age.

Grieve and colleagues[12] used estimates for early transition probabilities (from mild to moderate disease and from moderate disease to cirrhosis) derived from re-analysis of a dataset used in a previously published retrospective cohort study.[26] Data on 373 cases who attended St Mary's Hospital, London, between 1 January 1990 and 30 June 2001 and who had at least one biopsy were analysed. Patients with HCC, other types of liver disease in addition to hepatitis C, HIV co-infection or treatment prior to first biopsy were excluded. For the purposes of modelling disease progression mild chronic hepatitis C was defined as Ishak fibrosis stages F0–F2, moderate disease as stages

F3–F5 and cirrhosis as stage F6. Annual transition probabilities for forward transitions between consecutive states were estimated using maximum likelihood. Covariates associated with increased progression were male sex, older age at infection and alcohol consumption greater than 40 units per week – no significant association with viral genotype 1 was shown. As with the estimates developed by Bennett and colleagues,[88] these early transition probabilities are constant with respect to time. The estimates of fibrosis progression developed for the cost-effectiveness analysis of the UK Mild HCV trial presented by Grieve and colleagues[12] are lower than those estimated by Bennett and colleagues[88] and adopted by Davis and colleagues[90] and Wong and Koff[92] – and are lower than those applied in a preliminary analysis from the Mild Hepatitis C Trial team.[93]

The other major difference between models adopted in the included studies is whether decompensated disease is modelled as a single entity[12,93] or by separate clinical manifestations [ascites, variceal haemorrhage and hepatic encephalopathy (HE)].[88,90–92] This may have an impact on the clinical validity of the disease progression model, since large differences in mortality, quality of life and cost may be expected between the substates included under the heading 'decompensation' (see *Tables 32* and *33*). However, this is unlikely to have a substantial impact on the analysis of antiviral treatment for people with mild chronic HCV since most of their life expectancy will be spent in the early stages of liver disease. Assumptions about the rate of disease progression in the early stages of disease will have a far greater impact than decisions on the disaggregation of later disease states.

Estimation of costs within economic evaluations

Four of the included studies used the same resource use assumptions for their estimates of health state costs.[88,90–92] Bennett and colleagues[88] originally developed these assumptions based on estimates of the frequency of outpatient visits, laboratory tests and medication associated with each health state per year. Medication costs included in the health state costs are for treatment of decompensated disease, hepatocellular carcinoma and for liver transplant patients – costs of interferon treatment, both drug costs and costs for monitoring while on treatment, were estimated separately. Inpatient resource use was estimated based on observational data for hepatitis C patients undergoing hospitalisations related to hepatitis. These resource use estimates were used to develop a costing protocol detailing the frequency of use by resource type – inpatient and out-patient attendances, laboratory tests, endoscopy or scelotherapy. These estimates were subsequently adopted by Davis and colleagues,[90] Salomon and colleagues[91] and Wong and Koff,[92] who updated the cost estimates using appropriate pay and prices indices. Grieve and Roberts used published UK cost estimates for health state costs.[87,110]

The only study included in this review which used costs derived from observed data on resource use by patients in the relevant health states was that by Grieve and colleagues.[12] Costs for mild chronic hepatitis C and the SVR health state were estimated for patients included in the clinical trial.[65] An observational study, recruiting 183 patients with moderate disease and 175 patients with cirrhosis (compensated or decompensated), was conducted in order to cost the other health states in the model. Hospital resource use attributable to the relevant stage of hepatitis C was recorded based on medical records and computerised information systems.

Published economic evaluations – summary of methods

- A systematic review of cost-effectiveness studies identified only six economic evaluations of antiviral treatment for mild chronic hepatitis C. All studies used decision analysis of Markov models, extrapolating the effect of SVR on life expectancy and quality of life. Different definitions of SVR were used – early trials used sustained ALT normalisation as the outcome measure – and different definitions of mild disease.
- The evaluations were published between 1997 and 2005 and were conducted in the USA and UK. Studies involved IFN and dual therapy. Two recent publications also included PEG dual therapy as intervention.
- All studies indicate that antiviral treatment is effective in terms of improved life expectancy and quality-adjusted life expectancy compared with no antiviral treatment.
- Early intervention (treatment for mild disease) is cost-effective for genotype non-1 patients, but less likely to be so for genotype 1 patients, due to the lower SVRs observed for this subgroup.
- There are substantial differences in health state utilities applied in decision analytic models in chronic hepatitis C. Many published studies have used clinician-derived utility weights in the absence of patient-derived weights.

Health-related quality of life for patients with chronic hepatitis C

A literature search was undertaken to identify studies reporting health state values/utilities for individuals with chronic hepatitis C by stage of fibrosis. The details of databases searched and search strategy are documented in Appendix 5. The literature search identified two published studies reporting on health state values/utilities for patients with chronic hepatitis C by stage of fibrosis.[111,112] Health state values/utilities used in previous economic evaluations of antiviral treatment for patients with mild chronic hepatitis C are presented in the section 'Supporting information on quality of life associated with chronic hepatitis C' (p. 61), along with further supporting information on quality of life for patients with progressive liver disease associated with chronic hepatitis C.

Health state valuations

Chong and colleagues (2003):[111] Health state utilities and quality of life in hepatitis C patients

Consecutive patients attending the liver, liver transplant and hepatoma clinics at the University Health Network – a tertiary referral centre in Toronto, Ontario, Canada – were recruited over the period from mid-June to mid-August 2000. To boost the number of observations for patients who had achieved SVRs, additional subjects were recruited from clinic records of patients who had responded to antiviral treatment. The final sample included 193 subjects, with a mean age of 50.8 years and 68% of whom were men. Intravenous drug use was reported by 34% of all participants and 45% had received a blood transfusion prior to 1990.

A modified version of a standardised interview schedule for prostate patients[113] was used to elicit health state valuations for patients' current health state using a VAS and the standard gamble (SG) technique. Subjects also completed the Health Utility Index Mark 3 (HUI 3) and EuroQol Index. Subjects were classified into seven disease stages:

- SVR – negative qualitative PCR at least 6 months after treatment cessation (n = 36)
- mild or moderate chronic hepatitis C – liver biopsy showing METAVIR stage 0–3 (n = 44)
- compensated cirrhosis – liver biopsy or definite ultrasound computed tomography (CT) scan showing cirrhosis but no clinical signs of decompensation (n = 24)
- decompensated cirrhosis – at least one event of variceal haemorrhage, ascites or hepatic encephalopathy (n = 9)
- HCC – demonstrated by liver biopsy or CT scan (n = 15, with seven of these due to HCV, the rest with a mixture of aetiology)
- liver transplant (n = 30)
- no biopsy – without liver biopsy or biopsy more than 2 years old showing no cirrhosis (n = 35).

None of the subjects in the HCC group reported intravenous drug use and this group also had the smallest proportion having had a blood transfusion prior to 1990 – this probably reflects the mixed aetiology of HCC in this group. Among the mild/moderate chronic hepatitis C, compensated cirrhosis and decompensated cirrhosis groups 30% of patients had previously received interferon treatment and failed to respond – no analysis was presented of differences in quality of life or health state values between treatment-naïve patients and treatment non-responders.

The health state utilities measured using the different elicitation methods were significantly correlated with each other, with Spearman correlation coefficients ranging from 0.219 to 0.798. In the majority of cases the mean health state values decreased with advancing liver disease, with the lowest valuations for decompensated disease and HCC. The valuations derived using the VAS were consistently lower than those derived by other methods (except for HCC, where the HUI 3 value was lower than the mean VAS score). Valuations derived using SG tended to be higher than those derived using other methods, except for HCC, where the value was substantially higher than that for decompensated cirrhosis and almost equal to the value for patients post-liver transplantation.

Although the health state values decrease with advancing stage of disease, the differences between the mean utilities for disease stages were not found to be statistically significant – although the authors acknowledge that this may simply reflect the small sample sizes for the decompensated disease and HCC groups. Spearman rank correlation indicated that the trend in utility scores in relation to disease stage was significant (ρ = 0.222–0.322, $p < 0.006$). A possible confounding factor in this analysis was that the mean age increased with disease stage (from 44 years for the mild/moderate chronic hepatitis C group to 63 years for HCC). The authors report that although age adjustment reduced the trend, it was not removed.

Comparing their patient-derived values with those used in previous economic evaluations – all of

which used expert panel-derived values or only partially used patient data – the authors observed that the patient-derived values were generally lower (i.e. indicated greater quality of life impact) for the SVR and mild/moderate chronic hepatitis C stages and were higher (i.e. indicated less quality of life impact) for advanced disease stages. The range of values across disease stages was far narrower (0.18–0.26) than for expert-based values (0.40–0.83). They further noted that, for those measures where population norms are available (HUI 3 and EuroQol), the mean utility value for patients with SVR was similar to that for the general population using one measure (EuroQol), but not both. For the SVR patients in the sample SF-36 component scores only differed significantly from population norms on the general health component.

Sherman and colleagues (2004):[112] Health values of patients with chronic hepatitis C infection
A total of 124 patients with chronic hepatitis C were recruited from outpatient clinics at the University of Cincinnati Medical Centre. The sample included patients attending the liver transplantation clinic and an outpatient HIV treatment centre, and also general liver clinics. All subjects had confirmed HCV infection – diagnosed by serology and confirmed by HCV RNA testing or recombinant immunoblot assay. The mean age of the sample was 46.6 years and 64% were men.

HRQoL of subjects in the study was assessed using the Hepatitis Quality of Life Questionnaire[114] (the SF-36 supplemented by hepatitis C-specific questions). The Beck Depression Inventory was also administered, as previous research has reported an association between HCV infection and depression. Health state utilities were derived using a computer package (U-Maker) which elicits valuations using rating scales, time trade-off (TTO) and SG methods.

The mean score on the PCS of the SF-36 was 34.5 – this compares with a norm for the US population of 50 and agrees with previous research that suggested that quality of life is impaired for chronic hepatitis C patients compared with the general population.[50,115] Mean utility values for each valuation method were reported for the whole sample and by stage of disease. Overall mean utility values were 0.63, 0.83 and 0.79 for rating scales, TTO and SG, respectively. These results follow a pattern observed throughout this study, where the mean valuations were lower for rating scales than for TTO or SG, with the TTO and SG valuations being highly correlated. Health state valuations derived using rating scales were closely correlated with the MCS of the SF-36 ($r = 0.74$, $p < 0.001$), but not the PCS, whereas TTO and SG-derived valuations showed a weak correlation with the MCS ($r = 0.37$) and no correlation with PCS.

A significant difference in mean utility score was reported between patients with biopsy-confirmed cirrhosis and those confirmed without cirrhosis (0.51 vs 0.66, $p = 0.02$), but no similar difference was shown between TTO- and SG-based valuations. No consistent pattern of declining health state values was shown in relation to inflammatory activity, as determined by ALT. There was no difference between rating scale valuations for patients with compensated and decompensated disease, whereas TTO- and SG-derived valuations were substantially lower for decompensated disease (although this difference was not statistically significant).

All the subgroup analyses reported were undertaken in selected subsamples of the original study group. Only those patients whose disease stage was confirmed by biopsy ($n = 62$) were included in the comparison of cirrhotic to non-cirrhotic patients while only those with ALT testing 'in close temporal proximity' (undefined) to the interview date ($n = 55$) were included in the analysis of the impact of disease severity. The characteristics of patients included in these subsamples were not reported and their comparability cannot be assessed.

Multivariate analysis of the utility values derived by each method showed a strong negative association between Beck Depression Inventory score and utility values. This was the only factor that was a significant predictor for the utility values derived by all three methods. However, it is difficult to interpret these results as the method for dealing with observations with missing data for one or more variables in the analysis is not reported. For example, both ALT and presence of cirrhosis were included in the multivariate analysis, but only 55/124 subjects had valid data on ALT whereas 62/124 had data on liver biopsy.

The authors conclude that the study confirms previous research[50,115] which suggests that people with chronic hepatitis C have lower HRQoL than the general population. The absence of any consistent relationship between disease severity (as measured by ALT) and quality of life or health state values is also consistent with previous

TABLE 33 *Health state values/utilities[a] used in previous economic evaluations of antiviral treatment for mild chronic hepatitis C*

Health state	Bennett *et al.*[88b]	Davis *et al.*[90b]	Salomon *et al.*[91b]	Wong *et al.*[92b]	Grieve and Roberts[93b]	Grieve *et al.*[12c]
SVR		1.00			1.00	0.82
Mild disease	0.82	0.82	0.98	0.98	0.98	0.77 (0.66 on treatment)
Moderate disease	0.78	0.78	0.92	0.92	0.92	0.66
Compensated cirrhosis	0.70	0.70	0.82	0.82	0.82	0.55
Decompensated cirrhosis	Asc 0.35 VH 0.28 HE 0.30	Asc 0.35 VH 0.28 HE 0.30	Asc 0.65 VH 0.55 HE 0.53	Asc: ds 0.75 dr 0.52 VH 0.55 HE 0.53	0.50	0.45
Hepatocellular carcinoma	0.10	0.10	0.55	0.55	0.25	0.45
Liver transplant	Yr 1 0.50 Yr 2 0.70	Yr 1 0.50 Yr 2 0.70	0.86	0.86	NA	0.45

Asc, Ascites; dr, diuretic refractory ascites; ds, diuretic sensitive ascites; HE, hepatic encephalopathy; VH, variceal haemorrhaging.

[a] A utility value of 0 = death and 1 = perfect health.

[b] Valuations were derived from ratings by an expert clinical panel

[c] Valuations were derived from patient ratings of current health state. Responses to the EuroQol (EQ-5D) questionnaire were transformed to utility values using a standard tariff.[118]

studies[50,115,116] – although the authors do not acknowledge this or refer to this previous research. They argue that previous decision analyses and economic models, incorporating expert panel-derived health state valuations, overstate the differences in utility values across stages and severity of disease – citing Chong and colleagues[111] in support of this argument.

Supporting information on quality of life associated with chronic hepatitis C

Table 33 reports the health state values/utilities applied in previous economic evaluations of interferon treatment for patients with mild chronic hepatitis C. Bennett and colleagues[88] and Davis and colleagues[90] adopted the same model for their analysis, hence the same quality of life weights.

Similarly, Salomon and colleagues[91] adopted quality of life weights derived by Wong and colleagues for a previous decision analysis,[117] which were also used in the subsequent evaluation of treatment for mild chronic hepatitis C by Wong and Koff.[92]

The health state valuations used in previous economic evaluations of treatment for mild chronic hepatitis C vary substantially between studies. All published evaluations prior to Grieve and colleagues[12] used health state valuations based on the judgement of expert panels of clinicians rather than patients experiencing those health states. There is little consistency between the two sets of valuations (i.e. those originally developed by Bennett and colleagues[88] and by Wong and Koff[92]) derived from expert panels.

The clinician-derived valuations are dissimilar to the patient-derived valuations reported from the UK Mild HCV trial, which show a similar decrement in utility through diseases stages from mild chronic hepatitis C to decompensation. The reduction in health state valuations is approximately 0.1 at each stage of disease. In contrast, the values adopted in previous economic evaluations showed a distinct reduction in utility when moving from compensated cirrhosis to decompensated disease. Chong and colleagues[111] similarly showed smaller decrements between disease states up to compensated disease, but a more substantial decrease between compensated cirrhosis and decompensated disease.

These studies suggest economic evaluations of interventions for chronic hepatitis C need to take account of the reduction in patients' quality of life when modelling outcomes for all stages of disease,

but that severity of hepatitis infection (as assessed by ALT levels or level of viraemia) does not impact on quality of life. All studies suggest that quality of life is impaired even when in the asymptomatic state. Studies reporting patient-derived utilities show that health state utilities decrease with advancing liver disease, but that the difference in utilities may not be as great as has been assumed in studies using expert-based valuations. Studies suggest that the health state value for patients who have achieved an SVR is comparable to those for the general population of similar age.

Review of Roche submission to NICE (pegylated interferon alfa-2a)

Estimation of benefits

Model structure/structural assumptions

A state transition model was developed to model disease progression and treatment effects in mild chronic hepatitis C. The model is structurally similar to those used in previous economic evaluations[12,88,90–93] and is consistent with published studies of natural history. Decompensated disease is modelled as a single entity using data from a key source on disease progression and mortality in chronic hepatitis C patients. The relative merits of treating this as a single disease state or as separate clinical manifestations is not discussed in the submission.

The model includes seven health states:

- remission
- chronic hepatitis C (severity of disease defined by METAVIR fibrosis stages)
- cirrhosis (METAVIR stage F4)
- decompensated cirrhosis
- HCC
- liver transplantation
- death.

All patients start in the chronic hepatitis C health state – distributed roughly evenly (57 and 43%, respectively) between the no fibrosis (F0) and minimal scarring (F1) stages, which indicate mild disease using the METAVIR staging system. The natural history model has a proportion of patients progressing through increasing stages of fibrosis within the chronic hepatitis C health state toward the cirrhosis health state. Patients in these health states are not exposed to any condition-specific excess mortality and face only general population mortality risks. Patients who develop cirrhosis may progress to one of two health states (decompensated disease or HCC, both of which have an excess mortality risk) or may remain in the cirrhotic state. Patients with decompensated disease may be eligible for liver transplantation. This is not an allowed transition for patients with HCC, where the majority of patients will have died within 1 year of entering this state.

The primary outcome modelled is sustained viral response – defined as undetectable HCV RNA in serum 24 weeks after the end of treatment. The benefits of treatment are assumed to result only from changing patients' virological status, in that an SVR is regarded as a cure. Patients achieving an SVR enter the remission health state where they face no risk of progressive liver disease and are subjected only to general population mortality risks. Moreover, an SVR is associated with in increase in HRQoL, hence a higher utility value [see the section 'Health-related quality of life' (p. 63)] and has a health state cost of zero.

Patients who do not respond to treatment follow the pattern of disease progression as described by the natural history model. However, patients who fail to respond to treatment, but remain at the lowest stage of disease progression (METAVIR stage F0), may undergo a spontaneous remission of disease.

The lifetime horizon adopted in the model is appropriate given that the evaluation is concerned with treatments for a chronic disease which seek to avoid sequelae that result in significant impacts of patients' quality of life and also substantial excess mortality. The cycle length of 1 year is also appropriate given the comparatively slow rate of progression of disease.

Supporting data

The majority of the transition probabilities for progressive liver disease included in the natural history model are taken from a natural history study[119] and the previous economic evaluation by Bennett and colleagues.[88] Early transition probabilities, through METAVIR fibrosis stages from mild disease to cirrhosis, are taken from the economic evaluation by Salomon and colleagues.[91] These assume that progression rates are the same from mild to moderate disease and from moderate disease to cirrhosis, which does not accord with other evaluations reviewed earlier,[12,88,90,92] which have higher progression rates from moderate disease to cirrhosis than for mild to moderate disease.

The submission reports four main comparisons for patients with mild chronic hepatitis C, which are broken down by genotype. These are discussed in turn below.

Pegylated interferon alfa dual therapy and non-pegylated interferon alfa dual therapy
Two comparisons of PEG and IFN are reported:

- The first uses the early transition probabilities as reported by Salomon and colleagues[91] as estimates of fibrosis progression for patients with elevated ALTs. SVRs for PEG dual therapy in mild patients were derived for the subgroup of mild patients within the PEG 2a trial by Zeuzem and colleagues[66] and for IFN were taken from the UK Mild HCV trial.[65] The lifetime treatment costs and health outcomes were estimated separately by genotype and sex. These results were combined by applying the proportions of patients in each sex and genotype group included in the PEG 2a trial.[66]
- The second uses reduced fibrosis progression rates to estimate the cost effectiveness of intervention in patients with persistently normal ALTs. This is achieved by applying a relative rate estimate of 56%, derived from a longitudinal study of fibrosis progression in groups with elevated or normal ALTs,[120] to the fibrosis progression rates taken from Salomon and colleagues.[91] It should be noted that this risk reduction has been applied across all METAVIR stages. However, only patients in stages F0 to F2 were recruited to the study from which the RR was calculated. Otherwise the input data and calculations performed for this analysis are identical with those used for patients with elevated ALTs.

Pegylated interferon alfa dual therapy and best supportive care (no treatment)
The analyses described above were repeated, using the same input values for PEG 2a. A small proportion of patients within the best supportive care cohort may achieve spontaneous remission of disease, otherwise the natural history model of disease was used to estimate disease progression in this scenario.

Health-related quality of life

The utility values used in the submission are taken directly from the study of outpatients attending the liver, transplant and hepatoma by Chong and colleagues.[111] The values used in the cost-effectiveness analysis in the submission are those derived using the SG technique. These are higher than the values derived using other methods, although the authors reported that these differences were not statistically significant.

TABLE 34 *Health state utilities for chronic hepatitis C*

Health state	Chong and colleagues[111]
SVR	0.86
Mild chronic hepatitis C	F0 F1 0.79
Moderate disease	F2 F3 0.79
Compensated cirrhosis	F4 0.80
Decompensated cirrhosis	0.60
HCC[a]	0.72
Liver transplant	0.73

[a] *n* = 15: 7 with HCV, 4 with HBV, 3 with alcoholic liver disease and 1 with haemochromatosis.

Table 34 reports the utilities that were adopted for the Roche submission. Chong and colleagues'[111] analysis did not distinguish between mild and moderate disease when reporting health state valuations. For all valuation methods, except the rating scale, there was little difference between the utility values for mild/moderate disease and cirrhosis, but a substantial decrement in utility when moving from compensated to decompensated disease.

Estimation of costs

The costs applied in the submission were made up of two components. The costs of antiviral treatment were estimated separately from the health state costs used to estimate the lifetime costs of the medical management of chronic hepatitis C.

The drug costs for IFN dual therapy were based on a dosage of 3 MU three times per week (giving a weekly cost of £48.60) and 1000 mg of RBV daily (giving a weekly cost of £48.60). The treatment duration was 24 weeks for genotype 2/3, giving a total cost of £4130, and 48 weeks for genotype 1, giving a total cost of £8261. Drug costs for PEG 2a were based on a dosage of 180 µg/0.5 ml per week (giving a weekly cost of £132.00) and 800 mg of RBV daily (giving a weekly cost of £77). The treatment duration was 24 weeks for genotype 2/3, giving a total cost of £5016, and 48 weeks for genotype 1, giving a total cost of £10,032. The submission contains no estimate of any additional costs arising from the assessment and monitoring of patients (including laboratory tests and investigations) during treatment.

TABLE 35 *Health state costs from Roche submission*

State	Value (£)	Source
Remission	0	Assumption
Chronic hepatitis C	102	NICE Hepatitis C HTA report[121]
Cirrhosis	252	NICE Hepatitis C HTA report[121]
Decompensated cirrhosis	7,855	Expert Panel, previous submission
HCC	7,980	NICE Hepatitis C HTA report[121]
Liver transplant	46,551	NICE Hepatitis C HTA report[121]
Post-liver transplant	1,677	Expert Panel, previous submission

TABLE 36 *Cost-effectiveness of treatment with interferon alfa-2a (non-pegylated and pegylated): patients with fibrosis scores of F0 (57%) and F1 (43%), age 45 years (Roche submission)*

Treatment	Population	Incremental cost (£)	Incremental QALYs	ICER (£)
IFN 2a + RBV versus no treatment	Overall	4,743	0.71	6,677
	Genotype 1	5,832	0.43	13,583
	Genotype 2/3	2,966	1.17	2,538
PEG 2a + RBV versus IFN + RBV	Overall	1,353	0.48	2,793
	Genotype 1	1,931	0.49	3,949
	Genotype 2/3	410	0.48	860

Health state costs for the submission (*Table 35*) were taken from a published systematic review and from previous submissions to NICE, which were based on bottom-up costing using protocols based on expert opinion. The remission health state is assumed to have a zero cost. This is unlikely to be the case, at least in the short term, as patients are evaluated for durability of response post treatment.

Results

The submission presents cost-effectiveness estimates for interferon (both non-pegylated and pegylated) as dual therapy relative to no antiviral treatment and also for PEG dual therapy compared with IFN dual therapy for patients with mild chronic hepatitis C. This accords with the scope issued by NICE which identified both IFN and PEG (as dual therapy and monotherapy) as interventions for the appraisal and best supportive care as the comparator. However, this assumes that, if they are not treated with antiviral agents when their disease is at a mild stage, individuals whose disease progresses would never receive antiviral treatment. This does not accord with current NICE guidance,[125] which states that PEG dual therapy is recommended for treatment of adults with moderate to severe chronic hepatitis C. This suggests that patients whose disease progresses would ultimately be entitled to receive antiviral treatment. The impact of including a 'watchful waiting' option is addressed in this analysis [see the section 'SHTAC cost-effectiveness model' (p. 65)].

Table 36 reports the baseline cost-effectiveness estimates for PEG 2a. It suggests that antiviral treatment with interferon alfa (either non-pegylated or pegylated) as dual therapy with RBV is cost-effective relative to best supportive care. The lowest incremental cost effectiveness ratios are for genotype 2/3.

Patients in the baseline cohort are aged 45 years and have either no or minimal fibrosis (57% F0 and 47% F1). The cost-effectiveness ratios reported by Salomon and colleagues,[91] where the baseline cohort were all at fibrosis stage F0 at the beginning of the simulation, were substantially higher for antiviral treatment in mild chronic hepatitis C patients. This was because a large proportion of the cohort never developed progressive liver disease. This suggests that the baseline fibrosis distribution may have a large impact on estimates of the cost-effectiveness of antiviral treatment relative to best supportive care.

[Confidential information in the economics section of the Schering Plough submission to NICE on PEG 2b removed].

Chapter 6

Southampton Health Technology Assessments Centre (SHTAC) cost-effectiveness analysis

SHTAC cost-effectiveness model

Statement of the decision problem and perspective for the cost-effectiveness analysis

A model was developed to estimate the cost-effectiveness of PEG 2a and PEG 2b for the treatment of mild hepatitis C compared with current practice and best supportive care in a UK cohort of adults with mild chronic hepatitis C. The perspective of the cost-effectiveness analysis is that of the NHS and personal social services.

Strategies/comparators

The scope for the appraisal, as issued by NICE, states that the interventions to be considered are:

- dual therapy with PEG and RBV
- monotherapy (PEG) for those who cannot tolerate ribavirin;
- dual therapy with IFN and RBV.

The comparator for these interventions is stated as best standard practice, that is, treatment without any form of interferon therapy, which will be referred to as best supportive care. The scope also states that IFN should be considered as a comparator for PEG, where evidence allows.

The scope refers to current guidance on the treatment of moderate/severe chronic hepatitis C with pegylated interferons, but does not make explicit whether a 'watchful waiting' comparator should be included. Under this strategy, interferon treatment would be deferred until patients whose disease is currently mild progress to moderate/severe chronic hepatitis C and which would be covered by the existing guidance. This treatment strategy is included in this assessment report.

Model type and rationale for the model structure

The principal outcome of interest in the clinical trials reviewed in Chapter 4 is the SVR, defined as undetectable HCV RNA in the serum for at least 6 months after treatment cessation. To estimate the impact of this intermediate effect on final outcomes for patients, an appropriate model of the natural history of chronic hepatitis C was required. A systematic search was conducted of the literature to identify source material on the natural history, epidemiology and treatment of chronic hepatitis C (see Appendix 6 for details of the databases searched and the search strategy). References identified by these searches, along with previous economic evaluations reviewed in the section 'Results of the systematic review: cost-effectiveness' (p. 51), informed the development of a Markov state transition model. A new model was developed, rather than adopting the model used in the previous NICE appraisal of PEG dual therapy.[121] The original model did not distinguish between mild and moderate/severe chronic hepatitis C, would have required considerable adaptation in order to model early treatment against watchful waiting and adopted a fixed time horizon of 30 years. The underlying state transition model is the same, except that ascites, variceal bleed and HE (which were separate health states in the original model) have been collapsed into a single decompensated cirrhosis state and that background mortality transitions have been included for all states (in addition to the condition-specific mortality risks for those states that are associated with excess deaths).

The state transition diagram describing the seven health states within the model and the allowable transitions between these states is shown *Figure 1*. For clarity, mortality has not been included as a state within this transition diagram, though subjects in each health state are exposed to general population risks of mortality and some of the states represent excess mortality risks. In this diagram, ellipses indicate health states and arrows indicate allowable transitions between health states.

The state transition model indicates that, in the absence of successful treatment or the comparatively infrequent spontaneous remission of disease, an individual with mild chronic hepatitis C may remain in that health state or may progress to more severe stages of liver disease.

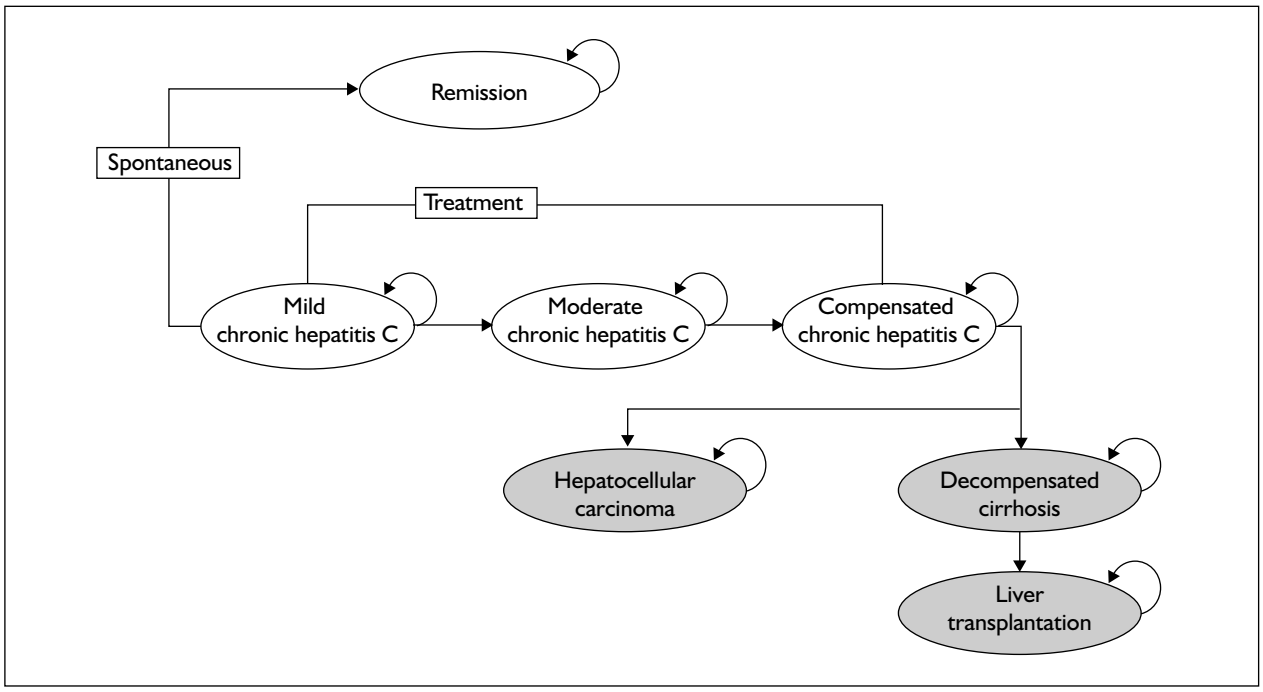


FIGURE 1 *State transition diagram*

The health state labelled remission in this diagram is synonymous with the SVR. This is assumed to be a permanent condition, with no spontaneous reactivation of disease, though individuals are not immune from re-infection. Individuals in this health state are assumed to face the same mortality risks as the general population and face no greater risk of liver cancer than the general population.

Patients in each of the mild and moderate chronic hepatitis C health states, and also compensated cirrhosis, face the same mortality risk as the general population. However, those with decompensated disease, HCC and who undergo liver transplantation face higher mortality rates than the general population. The shading of the ellipses for these health states indicates this.

In order to monitor patients' disease progression, a surveillance mechanism needs to be established for the watchful waiting strategy. It was assumed that patients have their initial staging of disease by liver biopsy. Under watchful waiting, those with mild disease enter the surveillance programme and will require periodic biopsies to determine disease progression and eligibility for antiviral treatment. The period between biopsies was initially set at 3 years, but was varied in the sensitivity analysis.

The model has a lifetime horizon and a cycle length of 1 year, with a half-cycle correction applied. To take account of adverse effects of antiviral treatment on HRQoL, health state utilities are reduced during the year in which treatment occurs. This occurs whether treatment is provided at the mild stage (early intervention) or at the moderate/severe stage (watchful waiting).

Baseline cohort of adult mild chronic hepatitis C patients

Baseline characteristics of adults with mild chronic hepatitis C are taken from the UK Mild HCV trial[65] with a mean age at infection of 25 years and mean age at entry to the model of 40 years. About 60% of the cohort is male and 50% of the cohort is genotype 1. The majority of the remaining 50% of the cohort are of genotypes 2 and 3, which is consistent with the predominant genotypes in England and Wales [see the section 'Background' (p. 3)].

Data sources

Effectiveness data

This report gives the findings from this systematic review on the clinical effectiveness of PEG [see the section 'Results' (p. 21)] and also the findings of the review of natural history models and clinical effectiveness data used in economic evaluations of interventions [see the section 'Estimation of outcomes within economic evaluations' (p. 54)].

TABLE 37 *Transition probabilities for natural history model*

Health state			
From	**To**	**Transition probability**	**Source**
Mild disease	Mild disease	–[a]	
	Moderate disease	0.025	Wright and colleagues,[65] Grieve and colleagues[12]
Moderate disease	Moderate disease	–[a]	
	Compensated cirrhosis	0.037	Wright and colleague,[65] Grieve and colleagues[12]
Compensated cirrhosis	Compensated cirrhosis	–[a]	
	Decompensated cirrhosis	0.039	Fattovich and colleagues[119]
	HCC	0.014	Fattovich and colleagues[119]
Decompensated cirrhosis	Decompensated cirrhosis	–[a]	
	HCC	0.014	Fattovich and colleagues[119]
	Liver transplant	0.020	Grieve and colleagues,[12] Siebert and colleagues[126]
	Death	0.130	Fattovich and colleagues[119]
HCC	HCC	–[a]	
	Death	0.430	Fattovich and colleagues[119]
Liver transplant	Liver transplant	–[a]	
	Death	Yr 1 = 0.210 Yr 2 = 0.057	Bennett and colleagues[88]

[a] This is the default transition and is calculated as the complement of the other transition probabilities for each health state.

TABLE 38 *SVRs (%) for interferon alfa dual therapy used for the base case analysis in the cost-effectiveness model*

SVRs used in model	IFN 2b	PEG 2a	PEG 2b
All patients	33	59	–[a]
Genotype 1	18	39	–[a]
Genotype non-1	49	78	–[a]

[a] SVRs for PEG 2b will not appear in all versions of this report. They were based on adjusted SVRs from Manns and colleagues' RCT,[17] as reported in the manufacturer's submission to NICE. **[Confidential information removed].**

Table 37 reports the transition probabilities adopted in the natural history model for this economic evaluation. They represent the complete set of transition probabilities for the best supportive care comparator. None of these transition probabilities is affected by treatment.

The transition probabilities for mild to moderate disease, and moderate disease to compensated cirrhosis were taken from a recent report which re-analysed data from UK cross-sectional and longitudinal datasets,[12,65] whereas the remaining transition probabilities were taken from the literature on natural history and previous economic evaluations.

Table 38 reports the treatment effects that have been applied to estimate the effectiveness of antiviral dual therapy with interferon (pegylated and non-pegylated) and RBV in the treatment strategies being considered.

SVRs for all patients, and by genotype, for IFN treatment of mild HCV were taken from the UK Mild HCV trial.[65] This trial evaluated IFN 2b; no trials of IFN 2a in patients with mild disease were identified.

The SVRs for PEG in patients with mild disease are based on two sources. For PEG 2b they were taken from the Phase III trial of PEG 2b by Manns and colleagues.[17] In this trial, the SVR for the subgroup of patients with no or minimal fibrosis was 61% [for patients treated with high-dose PEG – for more details of this trial, see the section 'Pegylated interferon alfa studies' (p. 43)]. The publication reporting the trial results does not give the SVR for the subgroup of patients with no or

TABLE 39 *SVRs (%) for interferon alfa monotherapy used for the base case analysis in the cost-effectiveness model*

SVRs used in model	IFN 2b	PEG 2a	PEG 2b
All patients	17	41	31
Genotype 1	6	31	14
Genotype non-1	28	50	47

minimal fibrosis by genotype. For this analysis, the SVRs by genotype, for patients with mild disease treated with PEG 2b, were taken from the manufacturer's submission to NICE (Wong J, New England Medical Center, Boston, MA: personal communication, 2005). The proportions of genotype 1 and genotype non-1 patients in the trial were different to those assumed for the UK population of chronic hepatitis C patients (68% genotype 1 and 29% genotype 2/3 compared with the 50:50 ratio assumed for this analysis). The reported SVRs for each genotype were used to adjust the overall SVR for all patients for the genotype distribution in the UK. For PEG 2a, SVRs were taken from the manufacturer's submission,[127] which reported SVRs for the subgroup of patients with mild disease within the PEG 2a trial by Zeuzem and colleagues.[66] The SVR for all patients was estimated based on the 50:50 ratio of genotype 1 and genotype non-1 assumed for the UK population of chronic hepatitis C patients.

Table 39 reports the treatment effects that have been applied to estimate the effectiveness of antiviral monotherapy with interferon (pegylated and non-pegylated) in the treatment strategies being considered.

SVRs, by genotype, for IFN monotherapy were taken from the trial by Lindsay and colleagues[73] [reviewed in the section 'Monotherapy trials' (p. 42)] as were the SVRs for PEG 2b. The SVRs for PEG 2a were taken from a trial reported by Reddy and colleagues.[72] Since the mix of genotypes in these trials did not match that assumed for the UK population of chronic hepatitis C patients, the SVRs for all patients were adjusted assuming a 50:50 ratio genotypes 1 and non-1.

For all these analyses it was assumed that, for both dual therapy and monotherapy, the same SVR applies for patients with mild disease receiving early treatment and those who wait to have active treatment once their disease has progressed to the moderate/severe stage. In the trials reviewed in the section 'Studies reporting subgroups of mild HCV patients' (p. 43), it appears that, where differences in SVRs have been reported, they tend to show higher responses in patients with mild disease. However, the majority have not reported tests of the statistical significance of these differences. Where statistical analyses have been reported, these have been inconsistent, with one trial reporting a significant difference and another reporting a non-significant difference. Given the lack of prospective RCT data on responses for patients receiving early treatment compared with watchful waiting, and the lack of strong within-trial evidence of differences in response between patients with mild and those with moderate disease, a conservative assumption was adopted that the same SVR would apply in both treatment strategies.

Health state values/utilities

The health state utilities adopted in the cost-effectiveness model are those estimated for the UK Mild HCV trial[65] (*Table 40*). Patients in the trial completed the EQ-5D at baseline, during treatment and during follow-up. The baseline assessments were used to estimate health state utility for patients with mild disease and the estimate for utility associated with SVR was based on responses at 24 and 48 weeks. Responses at weeks 12 and 24 for the treatment group of patients in the trial were used to estimate utilities for patients during treatment. A separate observational study recruiting 302 patients with varying severity of liver disease associated with chronic hepatitis C was undertaken to develop utility estimates for moderate disease and compensated cirrhosis.[12] Values derived from a UK study of costs and outcomes following liver transplantation were used for the decompensated cirrhosis, HCC health state.[128]

Discounting of future benefits

A discount rate of 1.5% was applied to future benefits. This is the current convention in UK cost-effectiveness analysis, and is in line with present guidance from NICE. A discount rate of 3.5% was applied in the sensitivity analyses.

TABLE 40 *Health state utilities*

Health state	Utility
SVR (from mild disease)	0.82
SVR (from moderate disease)	0.72
Mild chronic hepatitis C	0.77
Treatment for mild chronic hepatitis C	0.66
Moderate chronic hepatitis C	0.66
Treatment for moderate chronic hepatitis C	0.55
Cirrhosis	0.55
Decompensated cirrhosis	0.45
HCC	0.45
Liver transplant	0.45

Cost data

Costs in the model were developed in two stages. First, the additional resource use, in terms of laboratory tests, diagnostic tests and outpatient visits, required for monitoring patients while on treatment were identified based on clinical guidelines and discussion with hepatologists/specialist nurses at Southampton University Hospitals Trust. These are described below as intervention costs. Second, literature describing the costs of the progressive liver disease health states was reviewed and appropriate estimates applicable to the UK setting were extracted and used in the analysis.

Intervention costs

The frequency and intensity of monitoring of patients being treated with IFN and PEG were identified based on clinical guidelines and discussion with hepatologists/specialist nurses at Southampton University Hospitals Trust. Additional costs for patient management, including the initial evaluation of a new patient with chronic hepatitis C, further investigations required to assess suitability for treatment, costs of clinical decision-making regarding choice of treatment and final tests prior to commencing treatment, were also identified. These additional costs (described in full in Appendix 24) were applied in full to patients who were being evaluated prior to initiation of treatment, whereas for patients receiving best supportive care only the initial costs of evaluation of a new chronic hepatitis C patient were included.

All new patients are evaluated in the outpatient department, spending 1 hour with the specialist nurse and 20 minutes with the consultant, where they undergo an array of tests (described in Appendix 24), including screening for HCV and HBV, ultrasound scan of the liver and electrocardiogram. Those patients considered suitable for treatment require a further outpatient visit for review of initial evaluation results and HCV quantitative polymerase chain reaction (PCR) and test for HCV genotype. In addition, these patients will be admitted as a day case for a liver biopsy prior to the start of treatment.

It is assumed, in the watchful waiting strategy, that patients have their initial evaluation and are also assessed for treatment, as it is at this point that they undergo biopsy to stage their liver disease. As all patients in the model are initially at the mild stage of disease, none will be offered early treatment. These patients will require repeat biopsies to stage the progression of their disease. Those whose disease has progressed to the moderate/severe stage will then be offered antiviral treatment.

Patients treated with interferon alfa would be seen 10 times during a 24-week treatment period. This corresponds to weekly visits for the first month of treatment, then fortnightly for the second month and then monthly visits. Full blood counts, liver function tests, urea and electrolytes are assessed at each consultation. Every 3 months a more detailed assessment is undertaken during which HCV viral load and thyroid function is assessed. Standard consultations are assumed to take 30 minutes with the specialist nurse whereas the detailed assessments are assumed to involve more time with the consultant.

Patients treated with interferon alfa for 48 weeks would have six additional assessments. Full blood counts, liver function tests, urea and electrolytes are assessed at each consultation. Two of these additional assessments (at 36 and 48 weeks of treatment) are detailed assessments, including tests for HCV viral load and qualitative HCV RNA.

In addition to the excess costs of health service contacts for patients undergoing treatment, drug costs also need to be estimated. Drug unit costs were taken from the BNF No. 50 (September 2005).

Drug costs for IFN 2b (Viraferon) were calculated for a dosage of 3 MU, self-administered by patients three times per week using an injection pen. Cost per MU was estimated at £6, resulting in a weekly cost of £54. Total drug cost for 24 weeks of IFN monotherapy are therefore £1302 and cost for 48 weeks £2604.

Drug costs for RBV (Rebetol), used in dual therapy with PEG 2b and IFN, were calculated for a dosage of 1000 mg per day, based on an average body weight of 79 kg. A 168-tablet packet of

200-mg tablets costs £551.30, which corresponds to a weekly cost of £115. Combined with the costs estimated above, this gives a total drug cost for combination therapy (IFN 2b plus RBV) of £4058 for 24 weeks of treatment for genotype 2/3 and £8117 for 48 weeks of treatment for genotype 1.

Drug costs for PEG 2b (ViraferonPeg) were calculated for a patient weighing 79 kg (at a dosage of 1.5 µg/kg for dual therapy and 1.0 µg/kg for monotherapy). Weekly costs were estimated as the average of the unit cost for the appropriate dosage using a pre-filled pen and a vial (£109.62 for monotherapy and £158 for dual therapy). The total drug cost for a 24-week course of treatment for genotype 2/3 patients is £2631 for monotherapy and for 48 weeks £5261. The total drug costs estimated for 24 weeks of dual therapy are £6553 and £13,106 for 48 weeks of dual therapy.

Drug costs for PEG 2a (Pegasys) were calculated for a dosage of 180 µg/0.5 ml, self-administered by patients once per week, corresponding to a weekly cost of £132. The total drug cost for a 24-week course of treatment for genotype 2/3 patients is £3168 for monotherapy and for 48 weeks £6336. Drug costs for RBV (Copegus) for dual therapy with PEG 2a were calculated for a dosage of 800 mg per day for genotype 2/3 and 1000–1200 mg per day (depending on body weight, 1000 mg for weight <75 kg and 1200 mg for weight ≥75 kg) for genotype 1. A 168-tablet packet of 200-mg tablets costs £462.47. This corresponds to a weekly cost of £116 for genotype 1 (based on an average body weight of 79 kg) and £77 for genotype 2/3. The total drug costs estimated for 24 weeks of dual therapy are £5018 and for 48 weeks £11,886.

Health state costs

Table 41 presents health state costs. Health state costs for SVR, chronic hepatitis C, compensated cirrhosis, decompensated cirrhosis and HCC were taken from the observational study conducted during the UK mild HCV trial.[65]

Costs for liver transplantation and post-liver transplantation were taken from a DOH-funded study of the costs of liver transplantation.[129] Costs for 2002–3 were updated to 2003–4 costs using the Hospital and Community Health Services (HCHS) Pay and Prices Index.[130]

Discounting of future costs

A discount rate of 6% was applied to future costs. This is the rate that is used by convention in economic evaluations in the UK and is in line with current guidance from NICE. A discount rate of 3.5% was applied in the sensitivity analyses.

TABLE 41 *Health state costs*

Health state	Cost (£ per year) 2003–4 prices
SVR	267
Mild chronic hepatitis C	142
Moderate chronic hepatitis C	738
Compensated cirrhosis	1,171
Decompensated cirrhosis	9,385
HCC	8,363
Liver transplant	37,857
Post liver transplant	1,425

Presentation of results

Findings are reported on the cost-effectiveness of interventions based on analysis of a cohort of patients having age, sex and genotype characteristics as reported in the UK Mild HCV trial, as discussed earlier [see the section 'Baseline cohort of adult mild chronic hepatitis C patients' (p. 66)]. For the interventions being assessed in this report, comparisons for watchful waiting are made against best supportive care, whereas for early treatment the comparison is made against watchful waiting with the same antiviral agent (i.e. for early treatment with IFN dual therapy the comparison is made against watchful waiting with IFN dual therapy). Comparisons are also made for early treatment compared with watchful waiting with different agents.

The results of these comparisons are reported in terms of the incremental gain in QALYs and the incremental costs determined in the cohort analysis.

Assessment of uncertainty in the SHTAC analysis (sensitivity analysis)

Parameter uncertainty is addressed using probabilistic sensitivity analysis (PSA). Probability distributions are assigned to the point estimates used in the base case analysis. The point estimates for state transitions in the natural history and treatment effects are reported in *Tables 37* and *38* and for health state costs in *Table 41*. Distributions are also assigned to the health state utilities described in the section 'Health state values/utilities' (p. 68) and these are sampled during the probabilistic analysis. Appendix 25 reports the variables included in the PSA, the form of distribution used for sampling and the parameters of the distribution.

Univariate sensitivity analysis is used to address particular areas of uncertainty in the model related to:

- model structure
- methodological assumptions
- transition probabilities around which there is considerable uncertainty or which may be expected, *a priori*, to have disproportionate impact on study results.

The purpose of this analysis is to identify clearly the impact of this uncertainty and to test the robustness of the cost-effectiveness results to variation in structural assumptions and parameter inputs. Particular attention will be paid to key structural differences between models previously used in studies of the cost-effectiveness of antiviral therapy [reviewed in the section 'Results of the systematic review: cost-effectiveness' p. 51)] and the model adopted for this evaluation.

SHTAC cost-effectiveness model – summary of methods

1. A Markov state transition model was devised to estimate the cost-effectiveness of alternative treatment strategies for adults with mild chronic hepatitis C, from the perspective of the NHS and personal social services. This was based on the systematic review of literature on natural history, epidemiology and HRQoL in chronic hepatitis C, and also a systematic review of literature on clinical effectiveness and cost-effectiveness of antiviral treatment.
2. The treatment strategies evaluated are:
   (a) early antiviral treatment, for all patients with mild chronic hepatitis C, with either IFN or PEG
   (b) watchful waiting with antiviral treatment, provided only to those patients who progress to moderate/severe disease, with either IFN or PEG
   (c) no antiviral treatment and provision of best supportive care.
3. The model includes eight health states (SVR, chronic hepatitis C, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplant and death). Two 'tunnel' states within the chronic hepatitis C state distinguish severity of disease (i.e. mild or moderate/severe).
4. A cohort of patients pass through these states at different rates. The baseline cohort comprises patients with mild chronic hepatitis C, who have a mean age of 40 years and 60% of whom are male. In this cohort, 50% of patients are of genotype 1 and the majority of the remaining 50% are genotype 2 and 3.
5. The model has a lifetime horizon, with a cycle length of 1 year (with half cycle correction applied).
6. The short-term outcome of treatment is SVR. Estimates of SVRs following treatment were extracted from published trials and from unpublished data in the manufacturers' submissions. The model extrapolated the impact of SVR on life expectancy, quality-adjusted life expectancy and lifetime costs for the baseline cohort comprising patients with mild chronic hepatitis C under each treatment strategy.
7. Published quality of life weights estimated for a UK trial in patients with chronic hepatitis C were used to derive the QALYs associated with each treatment strategy.
8. To assess costs associated with antiviral treatment of chronic hepatitis C, resource use was estimated from clinical guidelines and advice from clinical practitioners. Drug costs were taken from the BNF. To estimate costs associated with the management of chronic hepatitis C, values from a UK trial in patients with chronic hepatitis C were used.
9. Costs were discounted at 6% and benefits at 1.5%.
10. Uncertainty was explored through probabilistic and deterministic sensitivity analysis.

Cost-effectiveness results

Cost-effectiveness findings are presented separately for the alternative treatment strategies using IFN dual therapy and PEG dual therapy for a cohort of chronic hepatitis C patients having the age, sex and genotype characteristics reported in the literature and described in the section 'Baseline cohort of adult mild chronic hepatitis C patients' (p. 66). Discounted costs are presented along with life expectancy and quality-adjusted life expectancy for patients in the cohort. Findings are presented for the incremental cost per life year gained and for incremental cost per QALY.

Base case results

Interferon alfa dual therapy (48 weeks of treatment)

Costs and outcomes modelled for IFN and PEG dual therapy for patients with mild hepatitis C are presented in *Table 42*. The assumed treatment duration for all patients in the base case is 48 weeks, regardless of genotype [the effect of

TABLE 42 *Base case cost-effectiveness for interferon alfa (non-pegylated and pegylated) and ribavirin (48 weeks of treatment)*

Treatment strategy		SVR	Cost (£)	Life-years	QALYs	Cost per QALY (£)
Best supportive care		0.00	5,989	27.94	20.17	
IFN 2b	Watchful waiting	0.33	8,532	28.18	20.55	6,585[a]
	Early treatment		13,476	28.20	21.16	8,092[b]
IFN 2b	Watchful waiting	0.49	7,942	28.30	20.80	3,097[a]
	Early treatment		12,581	28.34	21.72	5,043[b]
PEG 2a	Watchful waiting	0.59	8,346	28.38	20.94	3,052[a]
	Early treatment		14,834	28.41	22.04	5,900[b]
PEG 2b	Watchful waiting	–[c]	8,438	28.47	21.13	2,534[a]
	Early treatment		16,205	28.52	22.48	5,774[a]

[a] Comparing watchful waiting with best supportive care.
[b] Comparing early treatment with watchful waiting with the same agent.
[c] SVRs for PEG 2b will not appear in all versions of this report. They were based on adjusted SVRs from Manns and colleagues' RCT[17], as reported in the manufacturer's submission to NICE. **[Confidential information removed].**

adopting alternative durations of treatment is explored in the section 'Interferon alfa dual therapy – early stopping rules' (p. 76)]. This table reports total costs (antiviral treatment and supportive care), health outcomes (in terms of life-years and QALYs for each treatment strategy) and the incremental cost per QALY ratios for each intervention relative to their closest comparator. Costs are discounted at 6% and health outcomes at 1.5%.

Table 42 contains two entries for IFN 2b dual therapy. The first entry represents the model prediction using the 33% SVR observed in the UK Mild HCV trial.[65] A second set of estimates were derived using the overall SVR reported in Manns and colleagues' trial.[17] The overall SVR reported by Manns and colleagues[17] for IFN dual therapy was 47%, with an SVR of 49% for patients with no or minimal fibrosis. Both trials were used to allow cost–utility estimates to reflect the higher and lower range of SVRs reported in the literature.

The effect of this for the watchful waiting strategy is to increase the predicted outcome by 0.25 QALYs and to reduce lifetime costs by £590.

Table 42 shows that early intervention with IFN or PEG increases health gain (in terms of QALYs) but with substantially higher costs. The key differences between the strategies are that early treatment involves providing therapy to all patients with mild disease, some of whose liver disease will never progress to the moderate/severe stage. In contrast, the watchful waiting strategy involves providing antiviral treatment only to those patients whose disease progresses. Moreover, early treatment means that drug costs and excess costs for monitoring patients are all incurred in the first year of the strategy, rather than at a future date determined by the rate of disease progression.

Under the base case assumptions on disease progression, in the watchful waiting strategy, only 60% of the cohort of patients who initially have mild disease will progress to moderate disease and therefore receive active antiviral treatment. This difference in the proportion of the cohort undergoing active treatment means that, without taking into account the differential timing of antiviral treatment in the two strategies, drug costs are 40% lower for the watchful waiting strategy than for early treatment. When the difference in timing of antiviral treatment is taken into account, the average discounted cost for 48 weeks of IFN 2b dual therapy under watchful waiting is £2217 compared with £8117 for early treatment.

Table 42 shows that if the difference between SVRs for IFN dual therapy and PEG dual therapy are large, as is suggested by the comparison of the SVR reported from the UK Mild HCV trial (0.33) and those reported in trials sponsored by the drug manufacturers (0.59 to **[Confidential information removed]**), then much of the additional cost of treatment with PEG is offset by reduced lifetime costs for supportive care. Since the SVR health state is only associated with health care costs in the year immediately following treatment response (due to costs of post-treatment follow-up, viral assays and management of treatment-related

TABLE 43 *Life expectancy by health state by treatment strategy (life-years)*

Treatment strategy		SVR	Mild chronic hepatitis C	Moderate/ severe chronic hepatitis C	Compensated cirrhosis	Decompensated cirrhosis	HCC	Liver transplant	Total
Best supportive care		0.00	18.96	6.25	2.14	0.42	0.08	0.08	27.94
IFN 2b	Watchful	2.95	18.96	4.45	1.44	0.28	0.05	0.06	28.18
(SVR = 0.33)	Early treatment	9.22	12.94	4.21	1.44	0.28	0.05	0.06	28.20
IFN 2b	Watchful	4.42	18.96	3.54	1.08	0.21	0.04	0.04	28.30
(SVR = 0.49)	Early treatment	13.84	9.92	3.19	1.09	0.21	0.04	0.04	28.34
PEG 2a	Watchful	5.28	18.96	3.01	0.88	0.17	0.03	0.04	28.38
	Early treatment	16.53	8.16	2.60	0.89	0.17	0.03	0.03	28.41
PEG 2b	Watchful	6.45	18.96	2.30	0.60	0.12	0.02	0.02	28.47
	Early treatment	20.20	5.76	1.78	0.61	0.12	0.02	0.02	28.52

TABLE 44 *QALYs by health state by treatment strategy*

Treatment strategy		SVR	Mild chronic hepatitis C	Moderate/ severe chronic hepatitis C	Compensated cirrhosis	Decompensated cirrhosis	HCC	Liver transplant	Total
Best supportive care		0.00	14.60	4.13	1.18	0.19	0.03	0.04	20.17
IFN 2b	Watchful	2.15	14.60	2.83	0.79	0.13	0.02	0.03	20.55
(SVR = 0.33)	Early treatment	7.55	9.87	2.78	0.79	0.13	0.02	0.03	21.16
IFN 2b	Watchful	3.23	14.60	2.24	0.60	0.10	0.02	0.02	20.80
(SVR = 0.49)	Early treatment	11.33	7.55	2.10	0.60	0.10	0.02	0.02	21.72
PEG 2a	Watchful	3.86	14.60	1.89	0.48	0.08	0.01	0.02	20.94
	Early treatment	13.52	6.21	1.71	0.49	0.08	0.01	0.02	22.04
PEG 2b	Watchful	4.72	14.60	1.41	0.33	0.05	0.01	0.01	21.13
	Early treatment	16.53	4.37	1.18	0.34	0.05	0.01	0.01	22.48

adverse events which may persist for a period after treatment ceases), it follows that the greater the SVR then the greater is the potential saving in averted supportive care costs. When the SVR for IFN that was observed in Manns and colleagues' trial[17] is used to estimate cost-effectiveness, with a smaller disparity between SVR for IFN and PEG (0.49 vs 0.59 to **[Confidential information removed]**), the incremental cost-effectiveness ratio (ICER) for watchful waiting with PEG 2a compared with the same strategy for IFN becomes £2849 and for early treatment with PEG 2a compared with early treatment with IFN is £7007. The ICERs for the same comparisons with PEG 2b are £1477 (watchful waiting compared with the same strategy for IFN) and £4760 (early treatment with PEG 2a compared with early treatment with IFN). This contrasts with the situation where watchful waiting with both PEGs was cost saving, if the SVR for IFN was estimated at 0.33.

Table 42 also shows clearly that the QALY gain from early treatment is not derived from gains in life expectancy. While discounted life expectancy is greater for either treatment strategy than for best supportive care, for both IFN and PEG early treatment provides only a small increase in life expectancy (0.02–0.05 discounted life-years) compared with watchful waiting. The QALY gain under the early treatment strategy results from the expectation that an individual would spend a greater proportion of life expectancy in the SVR health state, on average, compared with watchful waiting (see *Tables 43* and *44*).

Table 44 shows that the SVR health state is associated with higher quality of life than the mild

chronic hepatitis C state. Therefore, treatment strategies that provide for a greater proportion of an individual's life expectancy in this health state will be associated with the greatest QALY gains, even where none of the strategies is associated with substantial increases in life expectancy.

The proportion of the cohort developing cirrhosis under the best supportive care strategy is 32%, whereas for IFN treatment the proportion of the population predicted to develop cirrhosis with watchful waiting is between 18 and 23% depending on SVR and between 16 and 22% for early treatment, depending on SVR. A similar pattern, where a smaller proportion of patients develop cirrhosis under the early treatment strategy, is shown for PEG (between 11 and 15% for watchful waiting, depending on SVR, and between 9 and 13% for early treatment).

Table 42 and *Figures 2–5* illustrate the incremental cost-effectiveness of early intervention and watchful waiting for patients with mild HCV treated with interferon alfa (non-pegylated and pegylated) dual therapy. The dashed line in *Figures 2–5* indicates the cost-effectiveness frontier, joining together the optimal treatment strategies – those which provide a given output at minimum cost. Points above the cost-effectiveness frontier are excluded, since the same output can theoretically be provided at lower cost by a combination of strategies that are found on the frontier.

Where the SVR for IFN dual therapy is 33%, both forms of PEG dominate IFN for the watchful waiting strategy, providing better outcome at lower cost (*Figures 2* and *4*). Early treatment with IFN is excluded as it does not lie on the frontier, where the SVR is at the low value of 33% (*Figures 2* and *4*). Where the SVR is at the higher value of 49%, early treatment with IFN dual therapy is not excluded from the optimal path when compared with PEG 2a.

The results of estimating the cost-effectiveness of early versus delayed antiviral treatment by genotype are presented in *Tables 45* and *46*. IFN dual therapy is estimated to provide only a small health gain for genotype 1 patients, due to the low SVR. Watchful waiting with IFN is associated with a high ICER, whereas early treatment provides a greater QALY gain, offsetting some of the increased cost.

For genotype 1, watchful waiting with PEG 2a has an ICER of £4668 compared with watchful waiting with IFN. Comparing early treatment with PEG 2a with early treatment with IFN has an ICER of £9984. Due to the higher SVR reported for PEG 2b, the QALY gain is greater for both watchful waiting and early treatment. The ICER for watchful waiting compared with watchful waiting with IFN is £1503 and for early treatment compared with early treatment it is £4803.

Given the higher SVRs for genotype non-1 patients, the health gains for each strategy are greater than for genotype 1. Watchful waiting with PEG 2a is cost saving if the SVR for IFN is at the lower level of 49% and has an ICER of £252 compared with watchful waiting with IFN if the

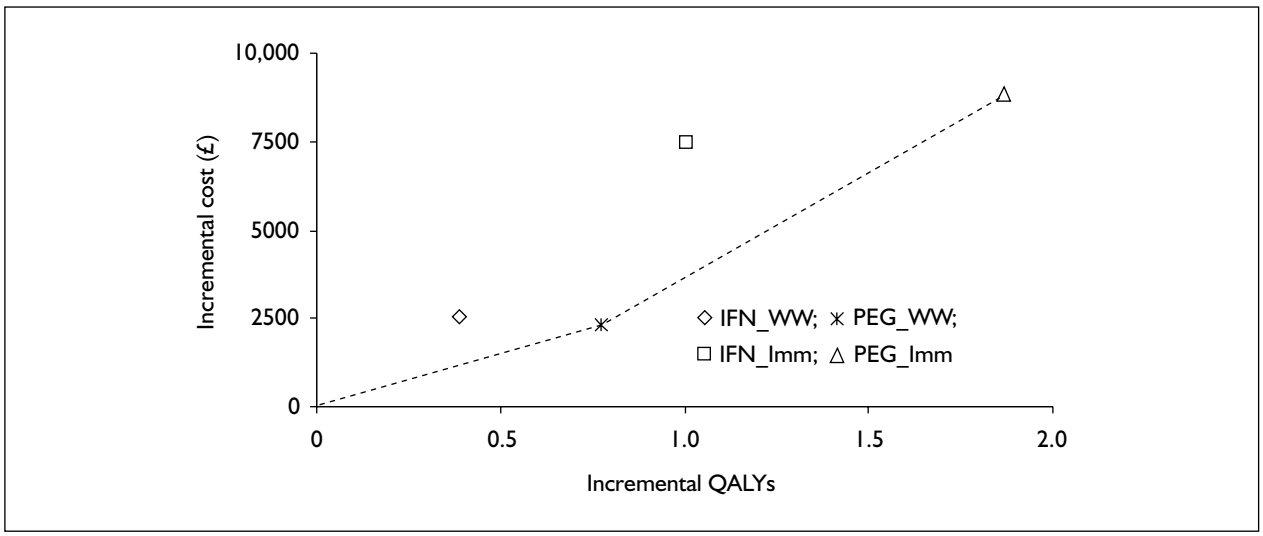


FIGURE 2 *Cost-effectiveness map: PEG 2a – IFN SVR = 0.33. Imm, early treatment; ww, watchful waiting.*

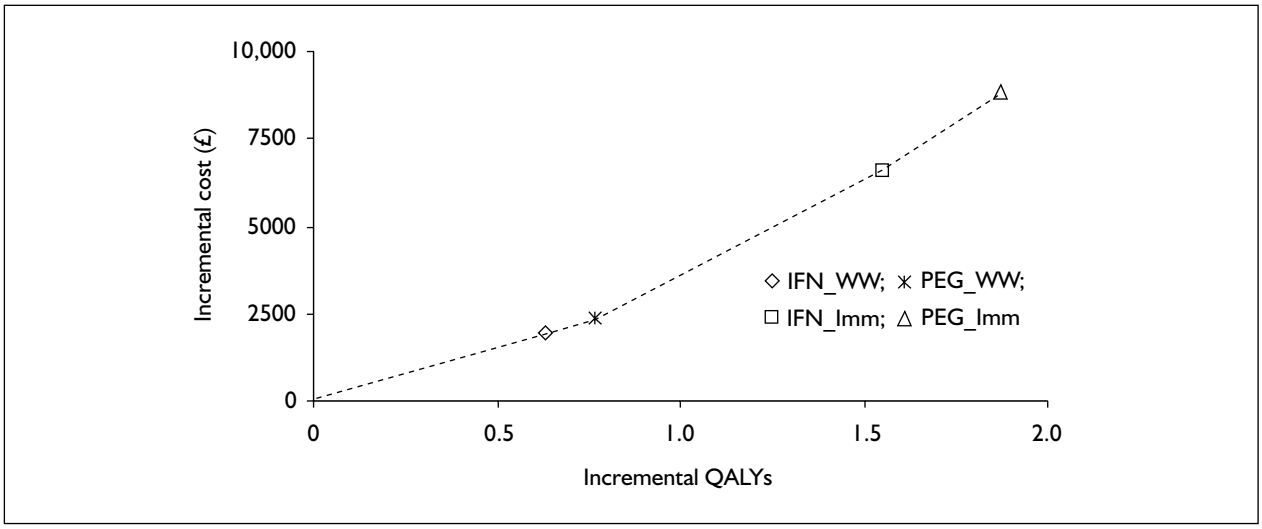


FIGURE 3 *Cost-effectiveness map: PEG 2a – IFN SVR = 0.49. Imm, early treatment; ww, watchful waiting.*

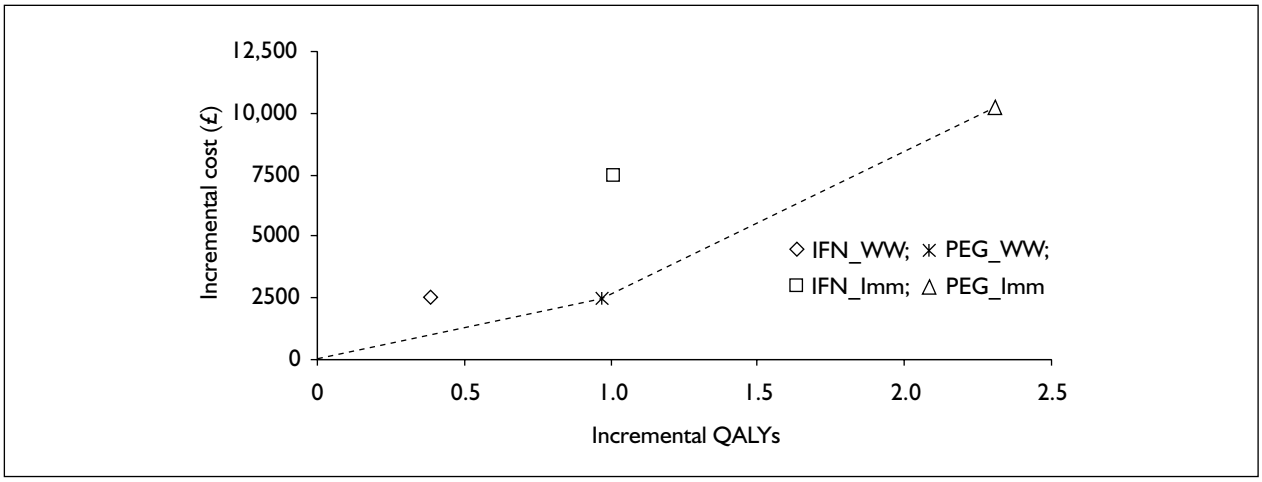


FIGURE 4 *Cost-effectiveness map: PEG 2b – IFN SVR = 0.33. Imm, early treatment; ww, watchful waiting.*

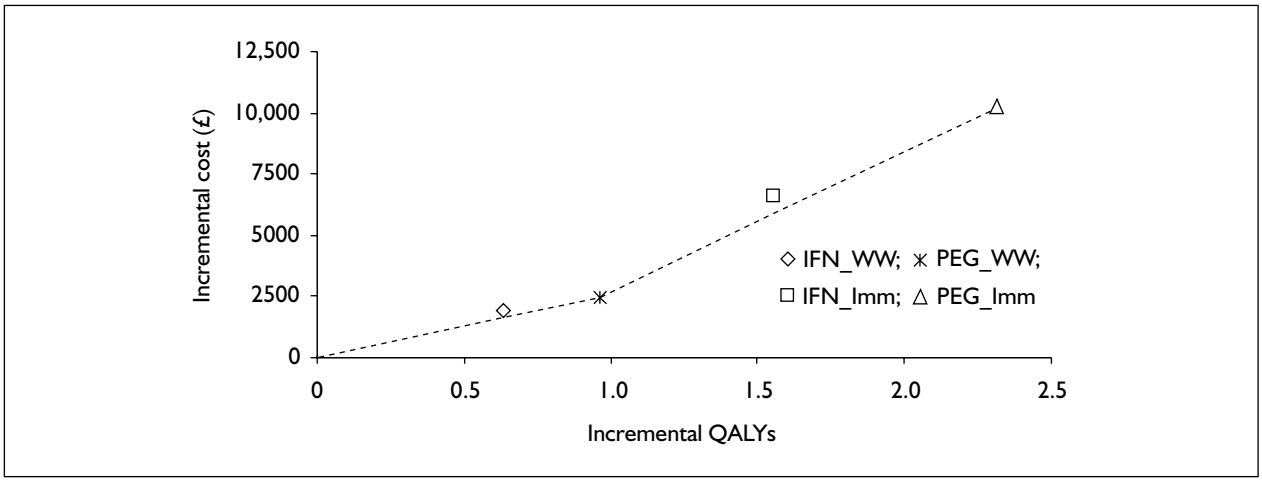


FIGURE 5 *Cost-effectiveness map: PEG 2b – IFN SVR = 0.49. Imm, early treatment; ww, watchful waiting.*

TABLE 45 *Base case cost-effectiveness for interferon alfa (non-pegylated and pegylated) and RBV for genotype 1 patients (48 weeks of treatment)*

Treatment strategy		SVR	Cost (£)	Life-years	QALYs	ICER (£)
Best supportive care		0.00	5,989	27.94	20.17	
IFN 2b	Watchful waiting	0.18	9,074	28.07	20.33	19,022[a]
	Early treatment		14,297	28.08	20.66	15,954[b]
IFN 2b	Watchful waiting	0.30	8,641	28.16	20.51	7,766[a]
	Early treatment		13,640	28.18	21.06	9,021[b]
PEG 2a	Watchful waiting	0.39	9,293	28.23	20.65	6,867[a]
	Early treatment		16,799	28.25	21.38	10,270[b]
PEG 2b	Watchful waiting	–[c]	9,143	28.33	20.84	4,670[a]
	Early treatment		17,273	28.36	21.82	8,324[b]

[a] Comparing watchful waiting with best supportive care.
[b] Comparing early treatment with watchful waiting with same agent.
[c] **[Confidential information removed]**.

TABLE 46 *Base case cost-effectiveness for interferon alfa-2a (non-pegylated and pegylated) and RBV for genotype non-1 patients (48 weeks of treatment)*

Treatment strategy		SVR	Cost (£)	Life-years	QALYs	ICER (£)
Best supportive care		0.00	5,989	27.94	20.17	
IFN 2b	Watchful waiting	0.49	7,944	28.30	20.80	3,105[a]
	Early treatment		12,584	28.34	21.72	5,050[b]
IFN 2b	Watchful waiting	0.65	7,351	28.43	21.04	1,558[a]
	Early treatment		11,687	28.47	22.27	3,528[b]
PEG 2a	Watchful waiting	0.78	7,399	28.52	21.23	1,326[a]
	Early treatment		12,868	28.57	22.70	3,725[b]
PEG 2b	Watchful waiting	–[c]	7,733	28.62	21.42	1,387[a]
	Early treatment		15,138	28.68	23.14	4,320[b]

[a] Comparing watchful waiting with best supportive care.
[b] Comparing early treatment with watchful waiting with same agent.
[c] **[Confidential information removed]**.

SVR is 65%. Comparing early treatment with PEG 2a with early treatment with IFN has an ICER of £2755. Again, the reported SVR for PEG 2b is higher than that for PEG 2a, resulting in a larger QALY gain for both watchful waiting and early treatment – the ICER for watchful waiting with PEG 2b compared with watchful waiting with IFN is £996 and for early treatment compared with early treatment is £3972.

Interferon alfa dual therapy – early stopping rules

The impact of early stopping rules on the cost-effectiveness of the alternative treatment strategies was investigated. The early stopping rules applied were based on early virological response (EVR) for genotype 1 and reducing the treatment duration to 24 weeks for all genotype non-1 patients.

Viral kinetic studies in clinical trial patients have shown that the majority of patients who achieve an SVR have responded to treatment by 12 weeks. There is a clinical consensus that patients who have not responded after 12 weeks of IFN should stop antiviral therapy. An analysis of pooled data from two clinical trials identified 12 weeks also as the optimum stopping date for PEG in patients who had not responded to treatment.[131] This approach offers economic benefits, in terms of reduced drug costs, but will also avoid utility losses for patients taking medication with significant adverse effects, from which they are unlikely to benefit.

In this analysis, the early stopping rule applied at 12 weeks for all patients who failed to achieve an early virological response. This was defined as

TABLE 47 *Base case cost-effectiveness estimates for interferon alfa and RBV, applying early stopping rules*

Treatment strategy		SVR	Cost (£)	Life-years	QALYs	ICER (£)
Best supportive care		0.00	5,989	27.94	20.17	
IFN 2b	Watchful waiting	0.33	7,678	28.18	20.57	4,153[a]
	Early treatment		10,308	28.20	21.21	4,135[b]
IFN 2b	Watchful waiting	0.49	7,087	28.30	20.82	1,684[a]
	Early treatment		9,413	28.34	21.76	2,464[b]
PEG 2a	Watchful waiting	0.53	7,546	28.34	20.87	2,200[a]
	Early treatment		11,447	28.37	21.88	3,896[b]
PEG 2b	Watchful waiting	–[c]	7,503	28.43	21.06	1,702[a]
	Early treatment		12,258	28.47	22.29	3,857[b]

[a] Comparing watchful waiting with best supportive care.
[b] Comparing early treatment to watchful waiting.
[c] **[Confidential information removed]**.

unquantifiable HCV RNA or a ≥2-log drop of HCV RNA from a patient's baseline measurement. These data are not reported by genotype in the journal report from the UK Mild HCV trial,[65] but are available in the full trial report to be published in the HTA series. This reports that 26 out of 40 genotype 1 patients with quantitative virology had unquantifiable HCV RNA or 2-log drop at 12 weeks, representing a proportion with EVR of 65%. In the trial, all patients who achieved SVR also had an EVR. Therefore, stopping treatment according to EVR was predicted to have no impact on the SVR for IFN, but would reduce the costs of treatment (by approximately 26% for average undiscounted drug costs).

The manufacturer's submission states that 21.8% of genotype 1 patients with mild disease failed to achieve an EVR on PEG 2a dual therapy in Zeuzem and colleagues' trial,[66] representing a proportion with EVR of 78.2%. Of the patients failing to achieve an EVR, one achieved an SVR through prolonged treatment. This requires a reduction in the SVR for genotype 1 patients from 38.5 to 37% for PEG 2a dual therapy with a 12-week early stopping rule.

There is no published information on EVR for genotype 1 patients treated with PEG 2b dual therapy in the trial reports. To estimate the impact of the 12-week stopping rule, the EVR reported from the pooled analysis of two trials of PEG (80%) was used.[131] In the absence of any data on the impact of this early stopping rule on SVR for PEG 2b, the same proportionate reduction in SVR (4%) as for PEG 2a was applied.

For genotype 2 and 3 patients, the treatment duration was reduced from 48 to 24 weeks. Data on SVR by treatment duration for the subgroup of patients with mild disease in Zeuzem and colleagues' trial[66] report an SVR following 24 weeks of PEG 2a dual therapy of 69%. There is no published information on the SVR for genotype 2 and 3 patients treated for 24 weeks with PEG 2b dual therapy. To estimate the SVR, the same proportionate reduction was applied as was observed for PEG 2a (11.5%).

Table 47 reports the cost-effectiveness estimates for interferon alfa dual therapy, after applying the early stopping rules. The application of early stopping rules has a substantial impact on estimated lifetime costs, with the effect being particularly marked for the early treatment strategy. Costs for the watchful waiting strategies typically reduce by around £700. However, costs for early treatment fall by around £3000. The effect on QALY outcomes is less dramatic. Treatment with interferon dual therapy was estimated to reduce the patient's health state utility by 0.11 while on treatment, due to side-effects and adverse events. This reduction in utility was assumed to apply only when the patient was treated – therefore, health state utility returned to the expected level for the health state when treatment ceased.

The order of reduction in lifetime costs is slightly lower for genotype 1 patients than for the mixed cohort of genotype 1 and genotype non-1. Costs of watchful waiting reduce by around £500 and for early treatment the reduction in cost is around £2000 (*Table 48*).

TABLE 48 *Base case cost-effectiveness estimates for interferon alfa and RBV, applying early stopping rules: genotype 1*

Treatment strategy		SVR	Cost (£)	Life-years	QALYs	ICER (£)
Best supportive care		0.00	5,989	27.94	20.17	
IFN 2b	Watchful waiting	0.18	8,485	28.07	20.37	12,443[a]
	Early treatment		12,113	28.08	20.69	11,104[b]
IFN 2b	Watchful waiting	0.30	8,052	28.16	20.55	5,402[a]
	Early treatment		11,457	28.18	21.10	6,172[b]
PEG 2a	Watchful waiting	0.37	8,821	28.22	20.65	5,850[a]
	Early treatment		14,925	28.24	21.36	8,646[b]
PEG 2b	Watchful waiting	–[c]	8,685	28.31	20.84	4,028[a]
	Early treatment		15,411	28.34	21.78	7,139[b]

[a] Comparing watchful waiting with best supportive care.
[b] Comparing early treatment with watchful waiting.
[c] **[Confidential information removed]**.

TABLE 49 *Base case cost-effectiveness estimates for interferon alfa and ribavirin, applying early stopping rules: genotype non-1*

Treatment strategy		SVR	Cost (£)	Life-years	QALYs	ICER (£)
Best supportive care		0.00	5989	27.94	20.17	
IFN 2b	Watchful waiting	0.49	6824	28.30	20.80	1327[a]
	Early treatment		8432	28.34	21.77	1653[b]
IFN 2b	Watchful waiting	0.65	6232	28.43	21.04	278[a]
	Early treatment		7534	28.47	22.32	1016[b]
PEG 2a	Watchful waiting	0.69	6352	28.45	21.10	391[a]
	Early treatment		8271	28.50	22.39	1478[b]
PEG 2b	Watchful waiting	–[c]	6321	28.55	21.28	300[a]
	Early treatment		9105	28.60	22.80	1826[b]

[a] Comparing watchful waiting with best supportive care.
[b] Comparing early treatment with watchful waiting.
[c] **[Confidential information removed]**.

The greatest reductions in cost are realised by applying a 24-week duration of treatment to genotype non-1 patients. Costs for watchful waiting reduce by approximately £1000 and for early treatment by approximately £4000. The effect of reducing treatment duration on health outcome is less marked, as shown in *Table 49*.

Interferon alfa monotherapy (48 weeks of treatment)

Costs and outcomes modelled for IFN and PEG dual therapy for patients with mild hepatitis C are presented in *Table 50*. The assumed treatment duration for all patients in the base case is 48 weeks, regardless of genotype. This table reports total costs (antiviral treatment and supportive care), health outcomes (in terms of life-years and QALYs for each treatment strategy) and the incremental cost per QALY ratios for each intervention relative to their closest comparator. Costs are discounted at 6% and health outcomes at 1.5%.

SVRs are lower than for interferon dual therapy, hence the estimated health gains are lower than for dual therapy. Although each treatment strategy is estimated to increase life expectancy, as with dual therapy, early treatment is not expected to offer substantial increases in life expectancy over watchful waiting (0–0.03 increases in life expectancy). The health gain expected with early treatment rather than watchful waiting arises from gains in quality of life as the cohort will spend more life expectancy in the SVR health state, as reported for dual therapy (see *Table 43*).

TABLE 50 *Base case cost-effectiveness for interferon alfa (non-pegylated and pegylated) monotherapy: all patients (48 weeks of treatment)*

Treatment strategy		SVR	Cost (£)	Life-years	QALYs	ICER (£)
Best supportive care		0.00	5,989	27.94	20.17	
IFN 2b	Watchful waiting	0.17	7,421	28.06	20.32	9,395[a]
	Early treatment		8,116	28.07	20.63	2,203[b]
PEG 2a	Watchful waiting	0.41	7,531	28.24	20.68	3,019[a]
	Early treatment		10,426	28.27	21.45	3,765[b]
PEG 2b	Watchful waiting	0.31	7,611	28.17	20.53	4,487[a]
	Early treatment		9,929	28.19	21.11	3,998[b]

[a] Comparing watchful waiting with best supportive care.
[b] Comparing early treatment with watchful waiting with same agent.

TABLE 51 *Base case cost-effectiveness for interferon alfa (non-pegylated and pegylated) monotherapy: genotype 1 (48 weeks of treatment)*

Treatment strategy		SVR	Cost (£)	Life-years	QALYs	ICER (£)
Best supportive care		0.00	5,989	27.94	20.17	
IFN 2b	Watchful waiting	0.06	7,819	27.98	20.15	Dominated
	Early treatment		8,718	27.98	20.26	8,390[b]
PEG 2a	Watchful waiting	0.31	7,893	28.17	20.53	5,265[a]
	Early treatment		10,973	28.19	21.11	5,313[b]
PEG 2b	Watchful waiting	0.14	8,225	28.04	20.27	20,773[a]
	Early treatment		10,860	28.05	20.53	10,196[b]

[a] Comparing watchful waiting with best supportive care.
[b] Comparing early treatment with watchful waiting with same agent.

For genotype 1 patients, watchful waiting with IFN monotherapy shows no gain in life expectancy, but a drop in quality-adjusted life expectancy (*Table 51*). This is due to the size of the utility decrement used to take account of side-effects and adverse events when receiving antiviral medication. The gains from responses to treatment are not sufficient to offset the quality of life impact of the treatment when the SVR is so low.

Outcomes are better for genotype non-1 patients, given the higher SVRs reported for this group (*Table 52*).

Sensitivity analysis

Univariate sensitivity analysis

A sensitivity analysis was conducted to consider the effect of uncertainty around model structure and for variation in certain key parameters that were expected, *a priori*, to be influential on the cost-effectiveness results. The method adopted is univariate sensitivity analysis, that is, varying one parameter at a time, leaving all other variables unchanged. This is to highlight the impact, if any, of each selected parameter alone on the cost-effectiveness results. The effect of uncertainty in multiple parameters was addressed using PSA, which is reported later in the section.

Table 53 reports the results of the sensitivity analysis for the overall cohort of patients. The table is divided to distinguish between analyses undertaken due to uncertainties in the model, uncertainties over the composition of the baseline cohort and uncertainty over parameter values.

A particular concern in performing the analysis of structural assumptions was to consider the impact of state transitions that have been included in previous economic evaluations of anti-viral therapy for mild chronic hepatitis C, but are missing from the model.

TABLE 52 *Base case cost-effectiveness for interferon alfa (non-pegylated and pegylated) monotherapy: genotype non-1 (48 weeks of treatment)*

Treatment strategy		SVR	Cost (£)	Life-years	QALYs	ICER (£)
Best supportive care		0.00	5,989	27.94	20.17	
IFN 2b	Watchful waiting	0.28	7,024	28.15	20.48	3,268[a]
	Early treatment		7,513	28.16	21.01	936[b]
PEG 2a	Watchful waiting	0.50	7,206	28.31	20.81	1,886[a]
	Early treatment		9,933	28.34	21.75	2,904[b]
PEG 2b	Watchful waiting	0.47	7,033	28.29	20.77	1,739[a]
	Early treatment		9,053	28.32	21.65	2,290[b]

[a] Comparing watchful waiting with best supportive care.
[b] Comparing early treatment with watchful waiting with same agent.

Previous economic evaluations [discussed in the section 'Results of the systematic review: cost-effectiveness' (p. 51)] and the industry models [discussed in the section 'Review of Roche submission to NICE (pegylated interferon alfa-2a)' (p. 62)] included the possibility of spontaneous remission of disease from the mild chronic hepatitis C health state. This is not included in the baseline model. When a spontaneous remission transition is included in the model it improves outcomes (in terms of life-years and QALYs) under the best supportive care strategy, thus reducing the incremental effectiveness of the antiviral treatment strategy that is compared with supportive care (IFN 2a dual therapy in this case). Including a spontaneous remission transition also improves outcome under the early treatment strategies by increasing the proportion of the cohort achieving an SVR, since those who fail to respond to treatment, but remain in the mild chronic hepatitis C health state, are eligible for spontaneous remission.

Changing the discount rates applied has a greater effect on the watchful waiting strategy than on early treatment. Reducing the discount rate from 6 to 3.5% has the effect of increasing the impact of costs borne in the future. As noted earlier, in addition to the difference in drug and monitoring costs between early treatment and watchful waiting due to differences in the proportion of the cohort of patients with mild disease expected to receive treatment over the model time horizon (100 versus 60%), there is a difference in the time at which the treatment strategies incur these costs. The early treatment strategy incurs all drug and monitoring costs in the first year of the model, whereas watchful waiting only incurs such costs in future years when disease progresses for a proportion of the cohort. In contrast, increasing the discount rate for outcomes, from 1.5 to 3.5%, has the effect of reducing the impact of future benefits. Therefore, any strategy that postpones costs and benefits will appear less cost-effective than early intervention as the discount rate for costs decreases and the discount rate for outcomes increases.

Changes in the characteristics of the baseline cohort have variable effects on the cost-effectiveness estimate. Varying the proportion of the cohort that is male has little effect on cost-effectiveness, but increasing the age of the cohort at the start of the simulation does have an effect. As age increases, all strategies appear less cost-effective, although this is more marked for watchful waiting.

The parameter that would be expected to have the greatest influence on cost-effectiveness estimates for antiviral treatment of chronic hepatitis C is the SVR associated with any treatment strategy. Clinical trials, reviewed in the section 'Results' (p. 21), have reported a wide range of estimates for the SVR for IFN (from 33 to 54%) among trials using the same dosage and duration of treatment. In the absence of head-to-head comparisons of IFN and PEG in patients with mild disease, it is necessary to make indirect comparisons. However, the variability in the SVR reported between trials makes such comparisons difficult.

Table 53 includes four entries to investigate the effect of reducing the differential between the SVR for IFN and PEG, both at the lower value observed in the UK Mild HCV trial[65] and at the higher value observed in the trial reported by Manns and colleagues.[17] Grieve and colleagues[12]

estimated ORs of SVR for PEG and RBV compared with IFN and RBV. These were based on the SVRs reported by Manns and colleagues.[17] The ORs were applied to the proportion of patients achieving SVR in the UK Mild HCV trial to infer an SVR for PEG 2b and RBV in routine UK clinical practice. These values (OR 1.43 for genotype 1 and 1.25 for genotype non-1, giving estimated SVRs for PEG 2a of 24 and 55%, respectively) were used in the first sensitivity analysis on SVR (scenario a in *Table 53*). The incremental cost per QALY gained for IFN does not change, since the base case SVR of 33% is being used. The ICERs for watchful waiting and immediate treatment with PEG are much greater than under the base case. For watchful waiting with PEG dual therapy, lifetime costs are £1200 higher than in the base case and quality-adjusted life expectancy is 0.5 lower, whereas for immediate treatment lifetime costs are almost £2000 higher than in the base case and quality-adjusted life expectancy has reduced by 1.1. The ICER for early treatment with PEG 2a compared with IFN is £23,252 – this contrasts with a value of approximately £2000 for the base case with the low SVR for IFN.

The second scenario to investigate the impact of the SVR involved increasing the differential between IFN and PEG 2b while keeping the SVR for IFN at its lower level (scenario b in *Table 53*). This second estimate of the SVR for PEG 2b used the same method of inference as described above. However, the OR on which it was based uses SVRs reported by Manns and colleagues[17] for patients receiving >10.6 mg/kg of RBV; 10.6 mg/kg is at the lower end of what is currently considered the optimal dose range. The ORs calculated for PEG 2b versus IFN are 1.77 for genotype 1 and 1.82 for genotype non-1, giving inferred SVRs of 28 and 64%, respectively, and an overall SVR of 45%. By increasing the difference between the SVR for IFN and PEG 2b this reduces the ICER for PEG 2b dual therapy compared with best supportive care. The ICER for watchful waiting with PEG compared with the same strategy with IFN is £4789. The ICER for early treatment with PEG compared with the same strategy with IFN is £10,183.

The above analyses were repeated for the higher SVR for IFN observed in the trial reported by Manns and colleagues[17] (scenario c in *Table 53*). This shows a similar but smaller increase in ICER compared with the base case. The ICER for early treatment with PEG 2a compared with IFN is £19,961 where the SVR for IFN is 49% and the SVR for PEG 2b is 56%. These analyses are reported only for PEG 2b since there are estimates of SVR only for IFN 2b, and there are no studies showing the relative effectiveness of IFN 2b and PEG 2a.

Increasing the disease progression rates increases the cost-effectiveness of all strategies. The higher rates used in this analysis are those adopted in previous economic evaluations of treatment for mild disease (see *Table 32*). Over the range of disease progression examined here – roughly doubling the transition probabilities from mild to moderate disease and from moderate to cirrhosis – the effect is not large. Reducing the cost of liver biopsy improves the cost-effectiveness of the watchful waiting strategy. Biopsy is assumed to be the surveillance mechanism for monitoring patients' disease progression and determining eligibility for treatment under watchful waiting.

Varying the health state utilities used in the model has a different impact between the early and delayed treatment strategies. Adopting the values presented by Chong and colleagues[111] has little impact on the ICERs for the delayed treatment strategies, but increases those for the early treatment strategies. The gain in utility from an SVR is similar to that reported by Grieve and colleagues,[12] which was adopted for this review. However, the health state utilities for more advanced stages of liver disease were not as low as those adopted for this review (see *Tables 33* and *34*).

Probabilistic sensitivity analysis

The PSA generated cost and QALY estimates for each intervention that were similar to those for the base case analysis (see *Table 42* for base case analysis). *Table 54* reports the mean costs and outcomes from the PSA, including the 2.5 and 97.5 percentiles to give an indication of the range of the simulated values, and the ICERs based on the values generated in the PSA.

Figure 6 shows the cost-effectiveness acceptability curves (CEACs) for the early treatment and watchful waiting strategies for IFN, PEG 2a and best supportive care. The chart indicates the probability that a given intervention is optimal compared with the other illustrated interventions. This suggests that at lower willingness to pay thresholds watchful waiting with PEG may be an optimal strategy, although early treatment strategies appear to be optimal strategies from a threshold around £7500 per QALY. Early treatment with PEG appears to be the optimal

TABLE 53 *Univariate sensitivity analysis results (all patients)*

	Cost per QALY (£)[a]							
	IFN Watchful waiting	**IFN Early treatment**	**IFN Watchful waiting**	**IFN Early Early treatment**	**PEG 2a Watchful waiting**	**PEG 2a Early treatment**	**PEG 2b Watchful waiting**	**PEG 2b Early treatment**
	SVR = 0.33		**SVR = 0.49**		**SVR = 0.59**		**SVR = –[b]**	
Baseline analysis	6,585	8,092	3,097	5,043	3,052	5,900	2,534	5,774
Structural assumptions								
Spontaneous remission of disease from mild chronic hepatitis C health state (0.002)	6,841	8,466	3,233	5,278	3,179	6,160	2,642	6,022
Spontaneous remission of disease from mild chronic hepatitis C health state (0.01)	7,966	10,043	3,829	6,266	3,735	7,245	3,113	7,058
Discount costs and outcomes at 3.5%	9,931	11,244	3,584	6,485	3,649	7,860	2,777	7,695
Baseline cohort characteristics								
Cohort 80% male (base case = 60%)	6,884	8,240	3,245	5,135	3,193	6,005	2,653	5,874
Cohort 40% male (base case = 60%)	6,292	7,942	2,953	4,950	2,913	5,795	2,416	5,672
Cohort 75% genotype 1 (base case = 50%)	10,045	10,685	4,907	6,687	3,412	6,846	3,412	6,846
Cohort 25% genotype 1 (base case = 50%)	4,365	6,209	2,273	4,246	2,184	4,912	1,885	4,959
Increasing age of cohort at start of simulation (base case = 40 years)								
–10 years	3,598	6,652	1,632	4,149	1,631	4,879	1,335	4,785
+10 years	15,127	10,962	7,129	6,812	6,839	7,894	5,705	7,691
+15 years	26,658	13,526	11,996	8,371	11,226	9,628	9,290	9,346
Parameter uncertainty								
(Scenario a) SVR IFN = 33% PEG = 38%	6,585	8,092					7,713	11,643
(Scenario b) SVR IFN = 33% PEG = 45%	6,585	8,092					6,010	9,829
(Scenario c) SVR IFN = 49% PEG = 56%			3,097	5,043			4,143	7,713

continued

TABLE 53 *Univariate sensitivity analysis results (all patients) (cont'd)*

	Cost per QALY (£)[a]							
	IFN Watchful waiting	**IFN Early treatment**	**IFN Watchful waiting**	**IFN Early Early treatment**	**PEG 2a Watchful waiting**	**PEG 2a Early treatment**	**PEG 2b Watchful waiting**	**PEG 2b Early treatment**
	SVR = 0.33		**SVR = 0.49**		**SVR = 0.59**		**SVR = –[b]**	
(Scenario d) SVR IFN = 49% PEG = 62%			3,097	5,043			3,425	6,862
Transition probability from mild to moderate disease = 0.04 (base case = 0.025)	4,947	6,069	2,112	3,803	2,231	4,459	1,869	4,368
Transition probability from moderate disease to cirrhosis = 0.073 (base case = 0.037)	3,921	8,684	1,691	5,419	1,686	6,341	1,350	6,208
Transition probability from mild to moderate disease = 0.04 and from moderate disease to cirrhosis = 0.073	2,881	6,575	1,036	4,139	1,136	4,857	898	4,765
Cost for SVR state = 0 (base case = £267 in first year after treatment ceases)	6,531	8,059	3,048	5,010	3,004	5,867	2,487	5,741
Cost of biopsy reduced by 50%	5,073	9,048	2,171	5,678	2,295	6,431	1,930	6,208
Biopsy every 5 years (base case = every 3 years)	5,848	8,331	2,433	5,309	2,482	6,094	2,052	5,929
Health state utility values from Chong and colleagues[111]	7,722	11,202	3,582	6,972	3,516	8,154	2,909	7,976
Reduce PEG costs by 20%	6,585	8,092	3,097	5,043	2,622	5,083	2,122	4,973
Reduce PEG costs by 30%	6,585	8,092	3,097	5,043	2,407	4,674	1,917	4,573
Reduce PEG and ribavirin costs by 20%	5,837	6,812	2,639	4,193	2,309	4,486	1,824	4,392
Reduce PEG and ribavirin costs by 30%	5,464	6,172	2,410	3,768	1,937	3,779	1,469	3,701

[a] All cost per QALY ratios are calculated on the same basis as in *Tables 42* to *52*. Watchful waiting strategies are compared with best supportive care and early treatment strategies are compared with watchful waiting with the same antiviral agent.
[b] **[Confidential information removed]**.

TABLE 54 *Costs and outcomes from PSA (all patients)*

		Discounted costs (£)			Discounted QALYs			Cost per QALY (£)
		Mean	2.5%	97.5%	Mean	2.5%	97.5%	
Best supportive care		5,926	4,653	7,342	20.16	19.23	21.05	
IFN 2a	Watchful waiting	7,902	6,773	9,137	20.81	20.42	21.15	3,042
	Early treatment	12,560	11,818	13,431	21.73	21.28	22.13	5,093
PEG 2a	Watchful waiting	8,305	7,151	9,595	20.95	20.58	21.25	3,011
	Early treatment	14,815	14,183	15,600	22.05	21.64	22.42	5,943
PEG 2b	Watchful waiting	8,639	7,344	9,924	21.05	20.11	21.88	3,224
	Early treatment	16,551	15,959	17,310	22.23	20.66	23.63	6,685

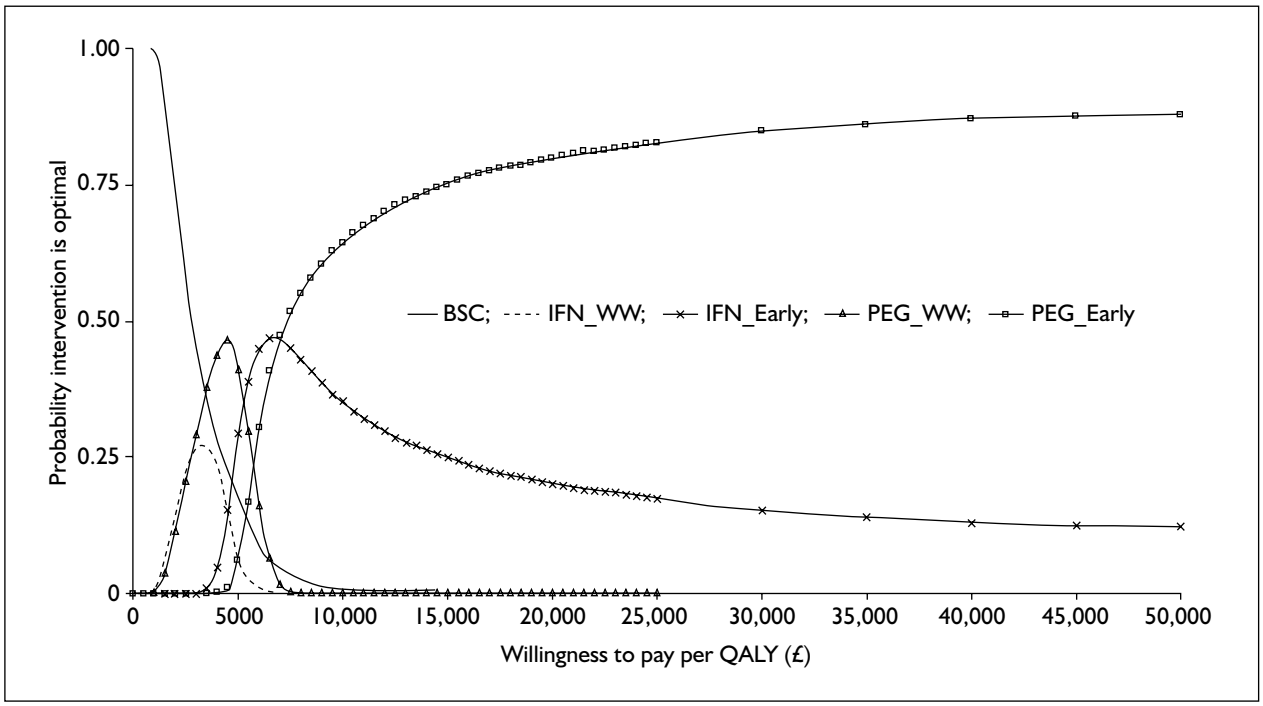


FIGURE 6 *CEACs for early treatment (Early) and watchful waiting (WW) with IFN and PEG 2a for mild chronic hepatitis C (all patients). BSC, best supportive care.*

intervention over a wide range of values for willingness to pay (which reflects the difference in SVR with PEG 2a against IFN in the data used in the evaluation), although there is a non-negligible probability that early treatment with IFN may be optimal.

Figure 7 shows the CEACs for the early treatment and watchful waiting strategies for IFN, PEG 2b and best supportive care. This chart is similar to *Figure 6* except that watchful waiting with PEG has a higher probability of being optimal across the range of values illustrated. Early treatment with PEG appears to be the optimal intervention over a wide range of values for willingness to pay (again, reflecting the difference in SVR with PEG 2b against IFN in the data used in the evaluation). However, both watchful waiting with PEG and early treatment with conventional IFN have a low, but non-negligible, probability of being optimal over the range of values shown.

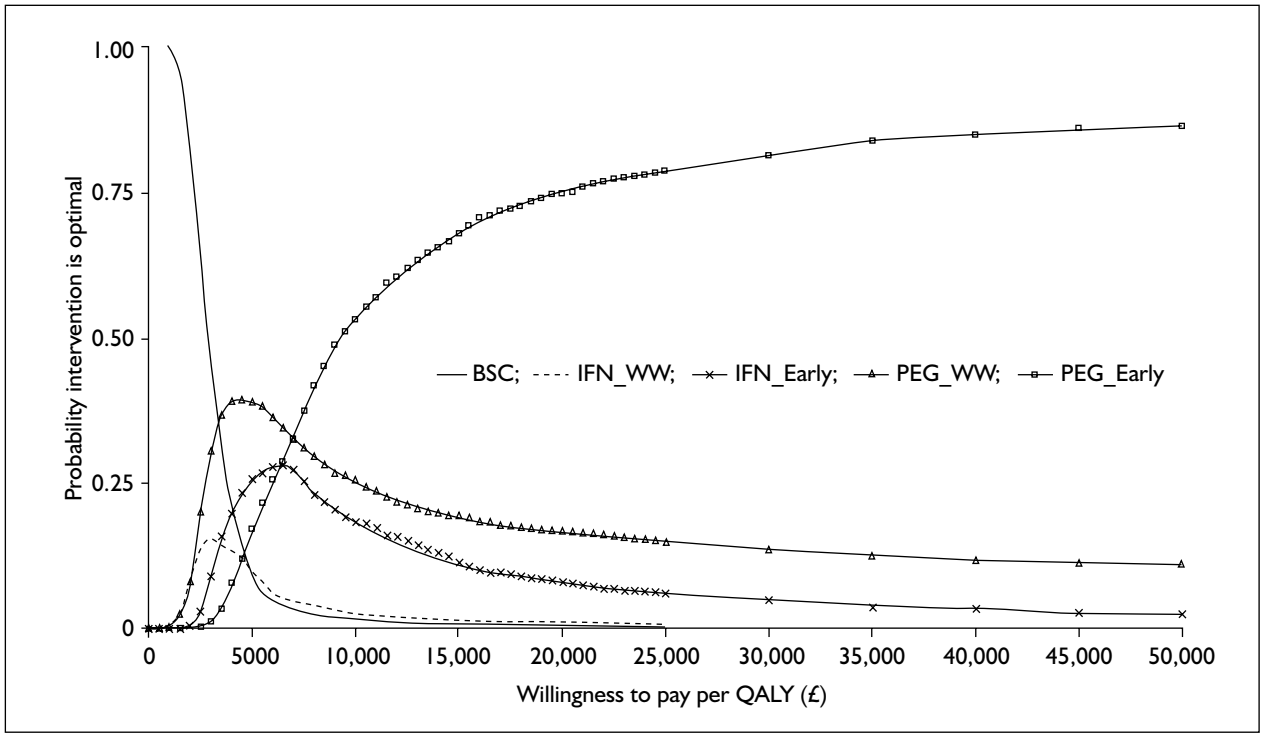


FIGURE 7 *CEACs for early treatment (Early) and watchful waiting (WW) with IFN and PEG 2b for mild chronic hepatitis C (all patients). BSC, best supportive care.*

Chapter 7

Implications for other parties

The social stigma attached to HCV, and for that matter many other infectious diseases, may act as a barrier to accepting treatment and, perhaps to a lesser extent, coming forward for assessment in the first place. Given that there are few obvious symptoms during the early stages of chronic infection (although some patients may experience impaired quality of life), there are few reasons why an individual, unless they are a health professional, for example, might need to disclose their status. However, the nature of antiviral treatment, which involves both oral and parenteral administration and some unpleasant adverse effects, will have a profound impact on a person's day-to-day living, making it harder to conceal their infection. Some may need to take time off work, which will have implications for their socio-economic circumstances. Some will also need support and care from families and partners.

The issuing of NICE guidance and the possible extension of antiviral treatment to a wider group of people may, to some extent, help to 'legitimise' the disease and, it is hoped, reduce the stigma associated with infectious diseases such as hepatitis. Hopwood and Southgate[132] review the international sociological literature on HCV and report that people living with hepatitis are often subjected to discrimination, particularly if the infection is acquired through injecting drug use or sexual contact. It is also suggested that there is an over-medicalisation of hepatitis at the expense of a more informed social and cultural understanding of the disease, and that risk groups such as IDUs are often assumed to be a homogeneous group when, in reality, they vary in terms of age, background and social and economic status. More research into the social and cultural impact of hepatitis is recommended, to inform effective prevention and management strategies.

In terms of the practicalities of commencing antiviral treatment, patients will need to learn how to inject themselves with interferon alfa. Specialist hepatology nurses will have a role in education and on-going support around injecting. Once weekly dosing of PEG is more convenient for patients than thrice weekly dosing of IFN. Health professionals and other agencies may also be involved in a health promotion capacity, working with the patient to prevent re-infection, particularly amongst IDUs.

Chapter 8

Factors relevant to the NHS

Identifying infections

Existing NICE guidance on the use of both PEG and IFN in the treatment of HCV will have undoubtedly raised the profile of antiviral treatment in the UK. Extension of this guidance to cover a wider group of patients will raise awareness further, potentially encouraging more people to present to health services for assessment and possible treatment. Guidance may help the DoH to fulfil its objective to increase awareness of HCV among the general public, as set out in the Hepatitis C Strategy (2002) and Hepatitis C Action Plan for England (2004). However, concerted efforts are needed to identify a greater proportion of the currently undiagnosed pool of infection ('active case finding'). Linked to this is the need to ensure equitable access to hepatology services, particularly for those who may be socially and economically disadvantaged. This will include some IDUs and some immigrants to the UK. Outreach services and specialist clinics, as used to target IDUs, may be appropriate. All new initiatives should be subjected to rigorous evaluation.

Referral and management

Efforts to identify anti-HCV infections need to be augmented by appropriate methods of referral to specialist care for further investigation and, if appropriate, antiviral treatment. As discussed in the section 'Antiviral treatment' (p. 13), a study in the Trent region of England found that only just over 50% of people who tested positive were appropriately referred.[57] A high proportion of those who were not referred were never informed of their test result. The proportion of patients with confirmed referral who progressed through the stages of the care pathway steadily diminished so that only 10% actually received antiviral treatment, with an estimated 5% achieving an SVR. Reasons for patient drop-out included logistical problems (e.g. patients moving to different areas of the country), service failure (e.g. patients not being told of their result) and patient choice/drop-out (e.g. not attending specialist clinics).

Clearly, greater efforts are needed to ensure an effective system of identification, referral and management to ensure that as many eligible people as possible have the opportunity to benefit from treatment. Irving and colleagues[57] call for more stringent procedures for referral, as is the case with other infectious diseases. Strategies are also needed to motivate patients to attend appointments and complete the full course of therapy. This may be more problematic for patients with mild HCV, who may not perceive their infection to be serious enough to undergo further assessment and treatment, particularly given the unpleasant adverse effects associated with interferon. Motivation is also particularly important for people who use drugs and alcohol, whose lifestyles are often unpredictable, making concordance with treatment regimes difficult. Such responsibilities may fall to specialist hepatology nurses, in addition to GPs and other services. However, these may be time and resource intensive, and will be subject to budget constraints.

Budget and resource impact

An increase in the number of patients eligible for antiviral treatment will have obvious budget implications for Primary Care Trusts who commission hepatology services. A recommendation to extend antiviral treatment to patients with mild HCV may dramatically increase the number of eligible patients in some areas. As reported in the section 'Incidence and prevalence' (p. 7), the proportion of patients with histologically mild disease in one English clinic-based cohort was 44%.

Adequate funding will need to be set aside to pay for an increased demand for drugs, although tailoring drug regimens according to patient characteristics (e.g. genotype) is likely to ensure more cost-effective use of resources. Although treatment is generally administered by specialist hepatology departments, commissioning and funding arrangements are complicated by the fact that a number of other agencies may be involved in the prevention, investigation, referral and management and rehabilitation of patients. These include primary care, genito-urinary medicine/sexual health services, drug and alcohol services, prison health services and specialist

agencies dealing with the health needs of high-risk ethnic groups. An integrated approach to commissioning is therefore desirable. The Foundation for Liver Research suggests the involvement of a nominated lead Primary Care Trust for liver disease, with involvement from Strategic Health Authorities and Regional Specialised Commissioning Groups.

Aside from budget considerations, capacity to deliver services is a key issue. If a larger number of eligible patients are successfully identified, assessed and offered to treatment, a greater number of specialist clinicians and specialist hepatology nurses will be required to meet this demand. It is questionable whether there is adequate capacity to deal with the potential rise in patient numbers. Expert clinical opinion suggests that some areas have difficulties in meeting demand already.

Managed Clinical Hepatology Networks

Effective implementation of national guidance on antiviral therapy may be facilitated by the National Plan for Liver Services,[53] which recommends that all patients receive treatment and care that are uniformly of high standard, via Managed Clinical Hepatology Networks (MCHNs). In particular, it is expected that MCHNs will show commitment in implementing NHS-directed research on evidence-based treatments. The plan also recommends accurate data collection to monitor clinical effectiveness to allow planning and adoption of best clinical practice and to permit comparison of patient outcomes across the country. It is envisaged that there will be 10–15 MCHNs in the UK, each responsible for between one and five million people. It is hoped that patients with liver diseases have equivalent access to specialist treatment as patients with renal or cardiac diseases.

Liver biopsy

The evidence from this report suggests that patients with histologically mild HCV can be treated effectively with antiviral therapy. This is particularly so for patients with favourable genotypes 2 and 3, in whom the proportion successfully treated reached as high as 80%. Consequently, there is less of a necessity to gauge disease severity to decide if treatment is necessary. The emphasis now is on when to treat, rather than whether to treat. Not all patients with mild HCV will want to be treated, at least in the short term. Some, such as genotype 1 patients, of whom only a relatively small proportion respond to treatment, may wish to wait until newer, more effective treatments are available. They will therefore require monitoring and further investigation over time to assess the extent of fibrosis progression and to initiate treatment if there is significant deterioration. One suggestion might be that panels of non-invasive biochemical tests and algorithms should be the first line, and only in cases of remaining doubt should liver biopsy be necessary. However, some clinicians still prefer to use biopsy as it provides additional useful information [as outlined in the section 'Use of biopsy' (p. 4)]. Practice is therefore likely to reflect clinician/patient choice. Evaluation of alternatives to biopsy, such as biochemical tests, is beyond the scope of this review, and therefore might be an appropriate topic for a future technology appraisal [see the section 'Research needs' (p. 94)].

Implementation

In terms of implementation issues, there do not appear to be any significant barriers to diffusion of the appraised treatments into routine practice. PEG (and to a lesser extent now IFN) is used routinely in practice, as is RBV. Specialist hepatology nurses will already be familiar with the administration of these drugs in the treatment of HCV.

Clinical guidelines

Finally, there is a need for updated UK guidelines to take into account the evidence from this report (and associated NICE guidance) and other emerging evidence for the effectiveness of antiviral treatment in patients with mild HCV. The BSG guidelines referred to throughout this report were published in 2001 (with a revision in 2003 to take into account PEG). Guidelines should be updated to address issues such as the use of biopsy, the emerging evidence for non-invasive tests, new evidence from clinical trials on studies in HIV–HCV co-infected patients,[133] and circumscribed treatment for subgroups of patients. A recently published RCT in patients with genotypes 2 and 3 with moderate to severe HCV reported that 12 weeks with PEG 2b and RBV was as effective as a 24-week course for those patients who had attained a viral response after 4 weeks of therapy.[134] Scottish guidelines are due to be published by the Scottish Intercollegiate Guidelines Network (SIGN) in 2006.

Chapter 9
Discussion

Clinical effectiveness

This effectiveness of antiviral combination therapy for mild HCV, as assessed in this report, was based on eight published RCTs. A further two RCTs report the effectiveness of PEG monotherapy. Few of these trials aimed specifically to assess the effectiveness of treating mild HCV, but nevertheless comprised cohorts of patients with low or minimal fibrosis. Details of 11 studies that included patients with both mild and moderate to severe HCV, and that reported results separately by severity, were also included.

Of the eight RCTs in the primary analysis, only three evaluated PEG (all PEG 2a). One of these, by Zeuzem and colleagues,[66] was originally designed to test the effectiveness of treating patients with PNALT levels. However, the majority of included patients showed evidence of mild fibrosis at baseline, enabling the study to be included in this review. Around half of the patients enrolled achieved an SVR when treated for 48 weeks, substantially reducing their risk of long-term liver disease. The SVR was even higher in another trial,[69] at 63% for a comparable treatment regimen (although the SVR is based on all patients in the trial, rather than the subset with histologically mild HCV). There were no RCTs of the other PEG (2b) that met the inclusion criteria. However, the trial by Manns and colleagues[17] was one of the 11 RCTs which reported results for subgroups of patients according to disease severity. The SVR for the subgroup of patients with no or minimal fibrosis at baseline was 57%, and reached 61% for patients given a higher dose of RBV. These trials show that patients with mild HCV can be effectively treated with both PEG 2a and 2b, in combination with RBV.

The remaining five RCTs in the primary analysis evaluated various regimens of IFN and RBV, the previous standard treatment. SVRs after 48 weeks of IFN 2b and RBV were in the range 33–54%. For 24 weeks of treatment the range was 36–69%. The latter was achieved in patients with very low baseline fibrosis (mean score of 0.5), treated for just 24 weeks, but with a much higher dose of IFN (6 MU) than commonly used.[67]

Interestingly, in the UK mild HCV RCT,[65] a trial designed specifically to evaluate treatment in this patient group, the SVR for IFN and RBV (33%) was relatively lower than that achieved by the other trials. Differences in response might be explained by heterogeneity between the trials, although all were multicentre RCTs comprising mostly middle-aged male patients, with generally comparable distributions of genotypes and with similar inclusion criteria. The SVR in the UK trial is also lower than reported for the same regimen in earlier trials of patients with moderate to severe disease. In our systematic review of IFN and RBV, published in 2000, the SVR for 48 weeks of treatment was 41% (95% CI 36 to 45) (based on a pooled analysis of two large multicentre RCTs of IFN 2b).[85] When the combination of IFN and RBV was evaluated as a comparator in the later licensing RCTs of PEG, SVRs were even higher, in the range 44–47%[11] (although it was recognised that these SVRs were unusually higher than previously reported). The other explanation is that the UK trial reflects a 'real world' scenario, whereby effectiveness is lower than often observed in large international multicentre trials conducted to support licence applications. This had implications for the assessment of cost-effectiveness [see the section 'Assumptions, limitations and uncertainties' (p. 93)].

No direct comparisons between PEG and IFN in histologically mild HCV patients were identified. This is in contrast to the moderate to severe HCV group, where a number of RCTs have compared the two. A direct comparison between the two interferons would have been helpful in this assessment. However, it is doubtful that such a trial would ever be commissioned. It is more likely that funds will be directed towards evaluating newer technologies for treating HCV [see the section 'Research needs' (p. 94)].

No RCTs were identified that evaluated 'early' treatment of histologically mild HCV patients compared with watchful waiting. However, such a trial would take years to complete, and may not be ethical given the emerging evidence for the effectiveness of antiviral treatment in patients with mild disease. Two of the eight RCTs in the

primary analysis reported viral response for subgroups of patients with mild and moderate to severe HCV.[63,69] In both trials, SVRs were higher for patients with low fibrosis, but only one of these reported statistical significance. A similar trend was observed in the 11 studies that reported subgroup analyses. However, few reported whether differences were statistically significant, and many of the studies were likely to be underpowered. For the purposes of the cost-effectiveness model, it was assumed that treatment in patients with mild HCV was of similar effectiveness to treatment of patients with more advanced disease [see the section 'Assumptions, limitations and uncertainties' (p. 93)].

As discussed in Chapter 2, much attention has been paid to the effectiveness of antiviral treatment in subgroups of patients with favourable and less favourable characteristics. The RCTs included in the primary analysis of clinical effectiveness reported virological response rates according to a number of these characteristics. In terms of genotype, the most commonly reported variable, SVRs tended to be higher in patients with the more favourable genotypes 2 and 3. In two of the PEG 2a trials, treating patients with these genotypes for 48 weeks yielded little or no additional benefit from treating for just 24 weeks. These results confirm what has been found previously in patients with more advanced disease, and are in line with current NICE guidance. That is, genotype 2 and 3 patients can be treated successfully with 24 weeks of PEG, whereas genotype 1 patients generally require 48 weeks.

There is emerging evidence to suggest that genotype 2 and 3 patients can be treated effectively after just 12 weeks. A recently reported RCT[134] (not meeting the inclusion criteria for mild HCV) randomised patients with this genotype to a standard 24-week course of PEG 2b with RBV, or to the same combination for 12 or 24 weeks, depending on whether tests for HCV RNA were negative or positive at week 4. The study concluded that 12 weeks of treatment can be recommended for those who respond at 4 weeks.

Some of the trials also reported virological response according to other patient characteristics. In two trials,[63,65] SVRs tended to be higher in patients aged less than 40 years, although differences were not statistically significant. Similarly, there were no statistically significant differences in SVR according to gender (measured in two trials.[63,65]) In one trial,[63] baseline ALT levels (raised or normal) did not have a significant effect on SVR rates. There has been discussion about the potential benefit of individualised treatment strategies, taking into account patient characteristics such as ALT, age, and genotype. Alberti[61] proposes treatment algorithms based on such factors [see the section 'Patients with persistently normal ALT' (p. 14)]. A recently published RCT evaluated a range of individualised treatment strategies based on viral response at 6 weeks of treatment with PEG 2a and RBV.[135] Patients were classed as having rapid, slow, flat or null viral response, and a treatment strategy was then prescribed accordingly. For example, some patients with a rapid viral response continued for only 24 weeks, whereas patients with null response continued with high-dose PEG. No additional benefit was observed for the individualised strategies compared with the control group who received standard treatment.

The generalisability of the findings of the RCTs to patients co-infected or with co-morbidities is limited. Patients with concurrent infections such as HIV and HBV and conditions such as haemophilia, diabetes and psychiatric disease tend to be excluded from clinical trials, making it difficult to assess what benefits these patients may derive. There is, however, a growing literature on the effectiveness of antiviral treatment in patients with HIV. The study by Chung and colleagues,[68] as described earlier, found that nearly 30% of co-infected patients with mild HCV achieved an SVR when treated with PEG 2a and RBV.

Cost-effectiveness

Our review of the literature identified six published economic evaluations of antiviral therapy for patients with mild chronic hepatitis C. The interventions evaluated varied between studies, depending on the available treatment regimen when the evaluations were undertaken. Three of the evaluations,[12,92,93] all concerned with the cost-effectiveness of interferon alfa combination therapy, examined the cost-effectiveness of early treatment (i.e. treatment at a mild stage of disease) against postponing treatment until patients develop moderate to severe disease. One of the evaluations estimated the reduction in 20-year incidence of cirrhosis from 27.5 to 18.4% by offering watchful waiting (with liver biopsy every 3 years and treatment for patients found to have progressed to moderate disease) compared with 16% for early treatment.[92]

Overall, the studies concluded that early treatment was associated with a gain in quality-adjusted life expectancy, but with additional costs. Early intervention involves treating a group of patients, not all of whom will progress to advanced liver disease. The early treatment strategy incurs all costs at the start of the programme in the expectation of reducing long-term health care costs. The extent to which this is realised depends crucially on the proportion of the initial cohort who respond to treatment, the rate of disease progression from mild to moderate and then to advanced disease and the relative costs attached to the advanced disease states as compared with those for mild disease and cure.

A model was developed to evaluate the cost-effectiveness of early intervention against watchful waiting with treatment for patients who developed moderate to severe disease. Supportive care was also required for those patients whose disease progressed following unsuccessful treatment and – under the watchful waiting strategy – those patients whose disease progressed to decompensated cirrhosis or HCC between assessments of their disease progression. In the model disease stage was assessed by liver biopsy every 3 years in a cohort of patients having the same characteristics as those in the UK Mild HCV trial.[65] Estimates of the effectiveness of antiviral treatment were based on the report from the UK Mild HCV trial and the manufacturers' submissions. Health state utilities and health state costs estimated in the UK Mild HCV trial were used to populate the model. Drug and on-treatment monitoring costs were estimated using standard dosing schedules and a set of patient management protocols.

In all cases, antiviral treatment was estimated to increase life expectancy over best supportive care. However, there was little difference in life expectancy between strategies using the same antiviral agent. Discounted life expectancy for the cohort offered IFN, and based on the SVR reported for the UK Mild HCV trial, was estimated to be 28.18 years for watchful waiting and 28.20 years for early intervention. The QALY gain associated with early treatment was 0.6, which comes from the expectation that a greater proportion of life expectancy would be spent in the 'cured' SVR health state and less in the mild disease state. The proportion of the cohort developing cirrhosis under best supportive care was 32%, whereas 18–23% were predicted to develop cirrhosis under watchful waiting and 16–22% under early treatment. Under the base case assumptions, PEG (both 2a and 2b) yielded superior QALY gains to IFN without a disproportionate increase in costs. This largely arose from the assumed large difference in SVR between IFN and PEG. The ICERs were sensitive to changes in key model parameters, including:

- the choice of discount rate
- the age at which the cohort starts the model
- fibrosis progression rates
- choice of health state utilities
- the proportion of genotype 1 and genotype non-1 in the cohort
- SVR.

Assumptions, limitations and uncertainties

A number of limitations and uncertainties have arisen during this assessment of clinical and cost-effectiveness.

First, the evidence base for the effectiveness of antiviral treatment in mild HCV is much smaller than that for more advanced HCV. Searches identified comparatively few published RCTs of treating mild HCV patients. The paucity of evidence for the effectiveness of treating mild HCV, combined with the heterogeneity in interventions, comparators and methods, also prohibited a meta-analysis.

Second, constructing a definition of mild HCV that could be used in the screening of eligible studies was problematic. Liver histology, via biopsy, appears to be the most accepted method of grading and staging the severity of HCV liver disease. As discussed in the section 'Biopsy classification systems' (p. 5), a number of biopsy classification systems exist, but they vary in scoring methods. Expert opinion and published literature enabled us to judge the comparability of the different classification systems and to develop a common threshold of histologically mild HCV. It was expected that very few clinical trials were likely to recruit exclusively mild patients. It was therefore necessary to define a threshold for the proportion of patients in a trial who were histologically mild. However, this is essentially an arbitrary decision. Yet, without setting a threshold there would have been very little evidence to include in this report. Further, it has to be accepted that the SVRs reported by the included studies reflect treatment outcome for up to 30% of patients with moderate to severe HCV. This may have the effect of underestimating the effect,

based on the notion that treatment effects are higher in patients with mild HCV. This has yet to be confirmed in a prospective head to head trial (and such a trial is unlikely to be commissioned).

The screening process was further hampered by poor reporting of the baseline histological profile of patients included in the potentially eligible studies. Just under half of the otherwise eligible reports retrieved for full screening were classified as unclear on this basis. Common problems were the failure to report baseline fibrosis scores (and in some cases any baseline histology at all) or not reporting which biopsy classification system was used. It is not possible to classify these studies without obtaining further information from the authors. However, it is expected that few of these studies would have included a sufficient proportion of mild HCV patients to qualify for the primary analysis [thus joining the RCTs presented in the section 'Trials of antiviral treatment in mild HCV patients' (p. 21)].

Third, the natural history of chronic HCV is poorly understood. There is a lack of good-quality epidemiological studies to inform an understanding of how the disease changes over time. Many of the published studies are subject to recall bias, measurement error and confounding. There has been particular uncertainty over whether or not patients with histologically mild HCV are at risk of progressing to more serious disease, or whether they remain in their mild, relatively benign state. Recent studies such as the Trent HCV cohort study have shown that mild HCV can be progressive.[34] However, there appears to be disagreement between studies on which patient characteristics correlate with fibrosis progression. Findings are mixed as to whether male gender and excessive alcohol consumption are linked to worsening disease, although there seems to be more agreement that advancing age is associated with accelerating progression. Further evidence from paired biopsy studies is needed, with larger cohorts and longer periods of follow-up. Unfortunately, it is becoming harder to recruit untreated patients into such studies, given the increasingly wider availability of effective antiviral treatment.

Fourth, the lack of head-to-head comparisons between PEG and IFN meant that the economic evaluation reported here made use of indirect comparisons, drawing information from a range of trials and selected subgroups. In the face of the variation in the SVRs observed for IFN, the evaluation considered high and low estimates for the SVR. Estimates of the SVR for PEG used data supplied by the manufacturers for patients with mild disease who were included in clinical trials of PEG and RBV. These SVRs are relatively high, especially in the context of the lower SVR for IFN observed in the UK Mild HCV trial. The effect of alternative assumptions for the SVR of PEG were explored in a sensitivity analysis and are reported in the section 'Sensitivity analysis' (p. 79).

The absence of prospective studies comparing treatment of histologically mild HCV patients with watchful waiting required assumptions to be made regarding the appropriate SVRs to apply for the treatment strategies being evaluated. Two factors to consider, in relation to the evaluation of early treatment and watchful waiting, are whether response to treatment is related to histological stage of disease and whether age at time of treatment may be important. Some of the trials included in the review reported higher responses in patients with mild disease and others reported higher response in younger patients (aged under 40 years), although the statistical or clinical significance of these findings was rarely reported. Given the lack of prospective data, or strong within-trial evidence, on treatment response in relation to either of these factors, a conservative assumption was adopted that the same SVR would apply for watchful waiting and early treatment strategies. Data to establish the validity of these assumptions would improve the credibility of models used to compare treatment strategies for subgroups of patient defined by histology or with differential timing.

Research needs

Assessment of clinical and cost-effectiveness of antiviral treatment in patients with mild HCV has identified the following research recommendations:

- Research and development need to be directed towards newer, potentially more effective interventions, particularly those that improve treatment response in patients with genotype 1, with minimal adverse effects. The National Horizon Scanning Centre recently reported that Thymalfasin (Zadaxin) is in Phase III trials for treatment of HCV patients not responding to previous therapy. If licensed it would be used in combination with PEG. An EU licence submission is expected in mid-2007.
- This assessment would have benefited from an RCT with economic evaluation comparing early

(mild HCV) treatment versus delayed (moderate to severe HCV) treatment. However, this may not be practical given the length of time such a trial would take.
- Further research into the natural history of HCV is required to estimate better the rate of liver disease progression. Larger cohorts need to be followed up for longer periods, with repeat biopsies (or alternative non-invasive investigations) where possible.
- Further research is needed into the effectiveness of non-invasive biochemical markers of liver disease, as an alternative to liver biopsy. This might be a suitable topic for a NICE appraisal of clinical and cost-effectiveness.

Chapter 10
Conclusions

This systematic review and economic evaluation has assessed the clinical effectiveness and cost-effectiveness of antiviral treatment in patients with mild HCV, a group previously not considered for therapy. This is the first time that treatment in this patient group has been examined at a policy level.

The evidence base for antiviral treatment in this patient group is relatively smaller than that for treatment in patients with moderate to severe disease. Nevertheless, eight RCTs of patients with predominantly mild HCV were included in the review. One of these was a UK-funded trial accompanied by economic evaluation in exclusively mild HCV patients. Up to 60% of patients with histologically mild HCV treated with PEG and RBV achieved an SVR. Between 33 and 69% of mild HCV patients treated with IFN and RBV, the previous standard treatment, also responded (depending on variations in dose and regimen). These response rates are broadly comparable to those achieved in patients with more advanced disease. Treating patients in the early, milder stages of HCV is therefore as clinically effective as it is when liver disease has progressed.

Results from economic modelling suggest that early treatment with PEG and RBV generally results in cost–utility estimates within the range considered by NHS decision-makers to represent good value for money.

Acknowledgements

The authors acknowledge Louise Baxter and Jill Colquitt of SHTAC and Linda Macyntire (independent researcher) for assistance with literature screening, Joanna Kirby of SHTAC for assistance with data extraction, Colin Green of SHTAC for advice on economic modelling and Cathy Benyon and the Finance Department of Southampton University Hospitals Trust for costing information.

Thanks are due also to the HTA mild UK HCV trial team for access to their publications. In particular, we would like to thank Richard Grieve for discussing the methodology used for modelling health economics outcomes and Professor Howard Thomas for general advice.

Expert advisory group

We are very grateful to our three anonymous peer reviewers and our advisory panel, who provided expert advice and comments on the protocol and/or draft of this report. The members of the advisory group were:

- Professor Roger Finch, Professor of Infectious Diseases, The City Hospital, Nottingham
- Dr Henry Watson, Consultant Haematologist, Aberdeen Royal Infirmary
- Dr Helen Howie, Consultant in Public Health Medicine, Grampian Health Board, Aberdeen
- Dr Stephen Ryder, Consultant Hepatologist, Queen's Medical Centre, Nottingham
- Dr Matthew E Cramp, Consultant Hepatologist, Derriford Hospital, Plymouth
- Dr John Morris, Services Development Manager, The Haemophilia Society, London.

Contribution of authors

Jonathan Shepherd (Principal Research Fellow) contributed to the development of the protocol, inclusion screening, data extraction/critical appraisal and drafting of the report. Jeremy Jones (Senior Research Fellow) contributed to the development of the protocol, inclusion screening, data extraction/critical appraisal, health economics and drafting of the report. Debbie Hartwell (Research Fellow) contributed to the development of the protocol, inclusion screening, data extraction/critical appraisal and drafting of the report. Peter Davidson (Visiting Senior Lecturer) contributed to the inclusion screening and drafting of the report. Alison Price (Information Scientist) was responsible for the literature searching and contributed to the drafting of the report. Norman Waugh (Professor of Public Health) contributed to the development of the protocol, health economics and drafting of the report.

This report was commissioned by the NHS R&D HTA Programme. The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA Programme. Any errors are the responsibility of the authors.

References

1. Mohsen AH, Trent HCV Study Group. The epidemiology of hepatitis C in a UK health regional population of 5.12 million. *Gut* 2001;**48**:707–13.
2. Balogun MA, Ramsay ME, Parry JV, Donovan L, Andrews NJ, Newham JA, *et al*. A national survey of genitourinary medicine clinic attenders provides little evidence of sexual transmission of hepatitis C virus infection. *Sex Transm Infect* 2003;**79**:301–6.
3. Mohsen AH, Easterbrook P, Taylor CB, Norris S. Hepatitis C and HIV-1 coinfection. *Gut* 2002;**51**:601–8.
4. Harris KA, Gilham C, Mortimer PP, Teo CG. The most prevalent hepatitis C virus genotypes in England and Wales are 3a and 1a. *J Med Virol* 1999;**58**:127–31.
5. Booth JC, O'Grady J, Neuberger J, Royal College of Physicians of London, British Society of Gastroenterology. Clinical guidelines on the management of hepatitis C. *Gut* 2001;**49** Suppl 1:i1–i21.
6. Dillon JF. Hepatitis C: What is the best treatment? *J Viral Hepat* 2004;**11** Suppl 1:23–7.
7. Royal College of Physicians/British Association for the Study of the Liver. *Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C – part review of existing guidance no. 75*. Submission to NICE on behalf of the Royal College of Physicians/British Association for the Study of the Liver. 2005.
8. The Hepatitis C Trust. *Submission to NICE for the partial review of existing guidance no. 75, assessing the use of interferon alpha and ribavirin in the treatment of mild chronic hepatitis C*. 2005.
9. The Haemophilia Society. *Submission to NICE for the appraisal of hepatitis C (mild to moderate) – pegylated interferons, ribavirin and alpha interferon*. 2005.
10. Shepherd J, Brodin HFT, Cave CB, Waugh NR, Price A, Gabbay J. Clinical- and cost-effectiveness of pegylated interferon alfa in the treatment of chronic hepatitis C: a systematic review and economic evaluation. *Int J Technol Assess Health Care* 2005;**21**:47–54.
11. Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J. Pegylated interferon a-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess* 2004;**8**(39).
12. Grieve R, Roberts J, Wright M, Sweeting M, DeAngelis D, Rosenberg W, *et al*. Cost-effectiveness of interferon α or peginterferon α with ribavirin for histologically mild chronic hepatitis C. *Gut* 2006;**55**:1332–8.
13. Colloredo G, Guido M, Sonzogni A, Leandro G. Impact of liver biopsy size on histological evaluation of chronic viral hepatitis: the smaller the sample, the milder the disease. *J Hepatol* 2003;**39**:239–44.
14. Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology* 2003;**38**:1449–57.
15. Kleiner DE. The liver biopsy in chronic hepatitis C: a view from the other side of the microscope. *Semin Liver Dis* 2005;**25**:52–64.
16. Dienstag JL. The role of liver biopsy in chronic hepatitis C. *Hepatology* 2002;**36** (5 Suppl 1): S152–60.
17. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R *et al*. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;**358**:958–65.
18. Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, *et al*. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). *Lancet* 1998;**352**:1426–32.
19. Wyatt J, Baker H, Prasad P, Gong YY, Millson C. Steatosis and fibrosis in patients with chronic hepatitis C. *J Clin Pathol* 2004;**57**:402–6.
20. Fartoux L, Chazouilleres O, Wendum D, Poupon R, Serfaty L. Impact of steatosis on progression of fibrosis in patients with mild hepatitis C. *Hepatology* 2005;**41**:82–7.
21. Desmet VJ. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, *et al*. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis [Hepatology 1981;**1**:431–435][comment]. *Journal of Hepatology* 2003;**38**:382–6.

22. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, *et al*. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology* 1981;**1**:431–5.

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

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

25. French METAVIR Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. *Hepatology* 1994;**1**:15–20.

26. Wright M, Goldin R, Fabre A, Lloyd J, Thomas H, Trepo C, *et al*. Measurement and determinants of the natural history of liver fibrosis in hepatitis C virus infection: a cross sectional and longitudinal study. *Gut* 2003;**52**:574–9.

27. Poynard T, Munteanu M, Imbert-Bismut F, Charlotte F, Thabut D, Le Calvez S, *et al*. Prospective analysis of discordant results between biochemical markers and biopsy in patients with chronic hepatitis C. *Clin Chem* 2004;**50**:1344–55.

28. Rosenberg WM, Voelker M, Thiel R, Becka M, Burt A, Schuppan D, *et al*. Serum markers detect the presence of liver fibrosis: a cohort study. *Gastroenterology* 2004;**127**:1704–13.

29. Balogun MA, Ramsay ME, Hesketh LM, Andrews N, Osborne KP, Gay NJ, *et al*. The prevalence of hepatitis C in England and Wales. *J Infect* 2002;**45**:219–26.

30. Department of Health. *Hepatitis C action plan for England*. London: Department of Health; 2004.

31. Health Protection Agency. *Shooting up – infections among injecting drug users in the United Kingdom 2003, an update: October 2004*. London: Health Protection Agency; 2004.

32. Harris HE, Ramsay ME, Heptonstall J, Soldan K, Eldridge KP. The HCV National Register: towards informing the natural history of hepatitis C infection in the UK. *J Viral Hepat* 2000;**7**:420–7.

33. Price D, Schmid M, Agarwal K, Hewett M, Craig W, Burt A, *et al*. Chronic hepatitis C in injecting drugs users: a comparison with non-injecting drugs users in the same geographic area. To be published.

34. Ryder SD, Irving WL, Jones DA, Neal KR, Underwood JC, Trent Hepatitis CSG. Progression of hepatic fibrosis in patients with hepatitis C: a prospective repeat liver biopsy study. *Gut* 2004;**53**:451–5.

35. Collier JD, Woodall T, Wight DG, Shore S, Gimson AE, Alexander GJ. Predicting progressive hepatic fibrosis stage on subsequent liver biopsy in chronic hepatitis C virus infection. *J Viral Hepat* 2005;**12**:74–80.

36. Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. *J Hepatol* 2001;**34**:730–9.

37. Poynard T, Mathurin P, Lai CL, Guyader D, Poupon R, Tainturier MH, *et al*. A comparison of fibrosis progression in chronic liver diseases. *J Hepatol* 2003;**38**:257–65.

38. Alberti A, Benvegnu L, Boccato S, Ferrari A, Sebastiani G. Natural history of initially mild chronic hepatitis C. *Dig Liver Dis* 2004;**36**:646–54.

39. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, *et al*. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis* 2001;**33**:562–9).

40. Mohsen AH, Easterbrook PJ, Taylor C, Portmann B, Kulasegaram R, Murad S, *et al*. Impact of human immunodeficiency virus (HIV) infection on the progression of liver fibrosis in hepatitis C virus infected patients. *Gut* 2003;**52**:1035–40.

41. Bayliss MS. Methods in outcomes research in hepatology: definitions and domains of quality of life. *Hepatology* 1999;**29** (6 Suppl):3S–6S.

42. Conry CC, VanRaden M, Gibble J, Melpolder J, Shakil AO, Viladomiu L, *et al*. Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. *N Engl J Med* 1996;**334**:1691–6.

43. Poynard T, Cacoub P, Ratziu V, Myers RP, Dezailles MH, Mercadier A, *et al*. Fatigue in patients with chronic hepatitis C. *J Viral Hepat* 2002;**9**:295–303.

44. Forton DM, Thomas HC, Murphy CA, Allsop JM, Foster GR, Main J, *et al*. Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. *Hepatology* 2002;**35**:433–9.

45. Forton DM, Taylor-Robinson SD, Thomas HC. Reduced quality of life in hepatitis C – is it all in the head? *J Hepatol* 2002;**36**:435–8.

46. Ware JE, Snow KK, Kosinski M, Gandek B. *SF-36 health survey: manual and interpretation guide*. Boston, MA: The Health Institute, New England Medical Centre; 1993.

47. Batts KP, Ludwig J. Chronic hepatitis. An update on terminology and reporting. *Am J Surg Pathol* 1995;**19**:1409–17.

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

49. Schwarzinger M, Dewedar S, Rekacewicz C, Abd Elaziz KM, Fontanet A, Carrat F, *et al*. Chronic hepatitis C virus infection: does it really impact health-related quality of life? A study in rural Egypt. *Hepatology* 2004;**40**:1434–41.

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

51. Hunt CM, Dominitz JA, Bute BP, Waters B, Blasi U, Williams DM. Effect of interferon-alpha treatment of chronic hepatitis C on health-related quality of life. *Dig Dis Sci* 1997;**42**:2482–6.

52. Ware JE, Bayliss MS, Mannocchia M, Davis GL, Bassaris H, Batey R, *et al.* Health-related quality of life in chronic hepatitis C: impact of disease and treatment response. *Hepatology* 1999;**30**: 550–5.

53. *National Plan for Liver Services UK: specialised services for hepatology and hepato-pancreato-biliary (HPB) surgery*. London: British Liver Trust, British Association for the Study of the Liver, British Society for Gastroenterology; 2004.

54. Shepherd J, Waugh N, Hewitson P. Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review. *Health Technol Assess* 2000;**4**(33).

55. Cramp ME, Rosenberg W. *Guidance on the treatment of hepatitis C incorporating the use of pegylated interferons*. URL: http://www bsg org uk/pdf_word_docs/pegylated_2003 doc. Accessed 17 June 2005.

56. Makris M, Baglin T, Dusheiko G, Giangrande PL, Lee CA, Ludlam CA, *et al*. Guidelines on the diagnosis, management and prevention of hepatitis in haemophilia. *Haemophilia* 2001;**7**:339–45.

57. Irving WL, Smith S, Cater R, Pugh S, Neal K, Coupland C et al. Clinical pathways for patients with newly diagnosed hepatitis C – what actually happens. *J Viral Hepat* 2006;**13**:264–71.

58. Seeff LB, Hoofnagle JH. National Institutes of Health Consensus Development Conference: Management of Hepatitis C: 2002. *Hepatology* 2002;**36**(5 I):S1–2.

59. Strader DB, Wright T, Thomas DL, Seeff LB, American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C. [Published erratum appears in *Hepatology* 2004;**40**:269.] *Hepatology* 2004;**39**:1147–71.

60. Schaefer M, Heinz A, Backmund M, Schaefer M, Heinz A, Backmund M. Treatment of chronic hepatitis C in patients with drug dependence: time to change the rules?. *Addiction* 2004; **99**:1167–75.

61. Alberti A. Towards more individualised management of hepatitis C virus patients with initially or persistently normal alanineaminotransferase levels. *J Hepatol* 2005;**42**:266–74.

62. NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews*. CRD Report Number 4. 2nd ed. York, York Publishing Services; York: 2001.

63. Mangia A, Villani MR, Minerva N, Leandro G, Bacca D, Cela M, *et al*. Efficacy of 5 MU of interferon in combination with ribavirin for naive patients with chronic hepatitis C virus: a randomized controlled trial. *J Hepatol* 2001; **34**:441–6.

64. Verbaan HP, Widell HE, Bondeson TL, Lindgren SC, Swedish HCV Treatment Group. High sustained response rate in patients with histologically mild (low grade and stage) chronic hepatitis C infection. A randomized, double blind, placebo controlled trial of interferon alpha-2b with and without ribavirin. *Eur J Gastroenterol Hepatol* 2002;**14**:627–33.

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

66. Zeuzem S, Diago M, Gane E, Reddy KR, Pockros P, Prati D, *et al*. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. *Gastroenterology* 2004;**127**:1724–32.

67. Cheng PN, Chow NH, Hu SC, Young KC, Chen CY, Jen CM, *et al*. Clinical comparison of high-dose interferon-alpha2b with or without ribavirin for treatment of interferon-relapsed chronic hepatitis C. *Dig Liver Dis* 2002;**34**:851–6.

68. Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, *et al*. Peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med* 2004;**351**:451–9.

69. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, *et al*. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;**140**:346–55.

70. Reichard O, Norkrans G, Fryden A, Braconier JH, Sonnerborg A, Weiland O. Randomised, double-blind, placebo-controlled trial of interferon alpha-2b with and without ribavirin for chronic hepatitis C. The Swedish Study Group. *Lancet* 1998;**351**: 83–7.

71. O'Brien C, Wintfeld N, Patel KK, Zeuzem S, Shiffman ML, Diago M, *et al*. The impact of sustained virological response (SVR) on health-related quality of life (HRQL) in patients with chronic hepatitis C (CHC) and persistently normal ALT levels (PNALT) treated with peginterferon alfa-2a (PEGASYS(R)) and ribavirin (COPEGUS(R)). *J Hepatol* 2004;**40** (Suppl. 1):147.

72. Reddy KR, Wright TL, Pockros PJ, Shiffman M, Everson G, Reindollar R, *et al*. Efficacy and safety of pegylated (40-kd) interferon alpha-2a compared with interferon alpha-2a in noncirrhotic patients with chronic hepatitis C. *Hepatology* 2001; **33**:433–8.

73. Lindsay KL, Trepo C, Heintges T, Shiffman ML, Gordon SC, Hoefs JC, *et al*. A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. *Hepatology* 2001;**34**:395–403.

74. Poynard T, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, *et al*. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. *Gastroenterology* 2002;**122**:1303–13.

75. Poynard T, McHutchison J, Davis GL, Esteban-Mur R, Goodman Z, Bedossa P, *et al*. Impact of interferon alfa-2b and ribavirin on progression of liver fibrosis in patients with chronic hepatitis C. *Hepatology* 2000;**32**:1131–7.

76. Schering-Plough Ltd. *ViraferonPeg in combination with ribavirin in the treatment of mild chronic hepatitis C in England and Wales – a submission to the National Institute for Health and Clinical Excellence*. Welwyn Garden City, Herts: Schering-Plough Ltd; 2005.

77. August-Jorg BS, Borovicka J, Dufour JF, Gonvers JJ, Henz S, Hermann R, *et al*. Twenty-four vs. forty-eight weeks of re-therapy with interferon alpha 2b and ribavirin in interferon alpha monotherapy relapsers with chronic hepatitis C. *Swiss Med Wkly* 2003;**133**:455–60.

78. Berg T, Hoffmann RM, Teuber G, Leifeld L, Lafrenz M, Baumgarten R, *et al*. Efficacy of a short-term ribavirin plus interferon alpha combination therapy followed by interferon alpha alone in previously untreated patients with chronic hepatitis C: a randomized multicenter trial. *Liver* 2000;**20**:427–36.

79. Hytiroglou P, Thung SN, Gerber MA. Histological classification and quantitation of the severity of chronic hepatitis: keep it simple! *Semin Liver Dis* 1995;**15**:414–21.

80. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology* 1994;**19**:1513–20.

81. de Ledinghen V, Trimoulet P, Winnock M, Bernard PH, Bourliere M, Portal I, *et al*. Daily or three times per week interferon alpha-2b in combination with ribavirin or interferon alone for the treatment of patients with chronic hepatitis C not responding to previous interferon alone. *J Hepatol* 2002;**36**:819–26.

82. de Ledinghen V, Trimoulet P, Winnock M, Foucher J, Bourliere M, Desmorat H, *et al*. Daily or three times a week interferon alfa-2b in combination with ribavirin or interferon alone for the treatment of patients with chronic hepatitis C. *J Hepatol* 2002;**36**:672–80.

83. Getachew Y, Browning JD, Prebis M, Rogers T, Brown GR. Combination therapy for the treatment of hepatitis C in the veteran population: higher than expected rates of therapy discontinuation. *Aliment Pharmacol Ther* 2004; **20**:629–36.

84. Mangia A, Santoro R, Piattelli M, Leandro G, Minerva N, Annese M, *et al*. High doses of interferon in combination with ribavirin are more effective than the standard regimen in patients with HCV genotype 1 chronic hepatitis. *J Hepatol* 2002;**37**:109–16.

85. Poynard T, McHutchison J, Goodman Z, Ling MH, Albrecht J, Poynard T, *et al*. Is an "a la carte" combination interferon alfa-2b plus ribavirin regimen possible for the first line treatment in patients with chronic hepatitis C? The ALGOVIRC Project Group. [Published erratum appears in *Hepatology* 2000;**32**:446]. *Hepatology* 2000;**31**:211–18.

86. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, *et al*. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. *N Engl J Med* 1998;**339**:1485–92.

87. Shepherd J, Waugh N, Hewitson P. Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review. *Health Technol Assess* 2000;**4**(33).

88. Bennett WG, Inoue Y, Beck JR, Wong JB, Pauker SG, Davis GL. Estimates of the cost-effectiveness of a single course of interferon-alpha2b in patients with histologically mild chronic hepatitis C. *Ann Intern Med* 1997;**127**:855–65.

89. Buti M, Casado MA, Fosbrook L, Wong JB, Esteban R. Cost-effectiveness of combination therapy for naive patients with chronic hepatitis C. *J Hepatol* 2000;**33**:651–8.

90. Davis GL, Beck JR, Farrell G, Poynard T. Prolonged treatment with interferon in patients with histologically mild chronic hepatitis C: a decision analysis. *J Viral Hepat* 1998;**5**:313–21.

91. Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Cost-effectiveness of treatment for

chronic hepatitis C infection in an evolving patient population. *JAMA* 2003;**290**:228–37.

92. Wong JB, Koff RS. Watchful waiting with periodic liver biopsy versus immediate empirical therapy for histologically mild chronic hepatitis C. A cost-effectiveness analysis. *Ann Intern Med* 2000;**133**: 665–75.

93. Grieve R, Roberts J. Economic evaluation for hepatitis C. *Acta Gastroenterol Belg* 2002;**65**:104–9.

94. Stein K, Rosenberg W, Wong J, Stein K, Rosenberg W, Wong J. Cost effectiveness of combination therapy for hepatitis C: a decision analytic model. *Gut* 2002;**50**:253–8.

95. Davis GL, Balart LA, Schiff ER, Lindsay K, Bodenheimer HC Jr, Perrillo RP, *et al*. Treatment of chronic hepatitis C with recombinant alpha-interferon. A multicentre randomized, controlled trial. The Hepatitis Interventional Therapy Group. *J Hepatol* 1990;**11** (Suppl 1):S31–5.

96. Lindsay KL, Davis GL, Schiff ER, Bodenheimer HC, Balart LA, Dienstag JL, *et al*. Response to higher doses of interferon alfa-2b in patients with chronic hepatitis C: a randomized multicenter trial. Hepatitis Interventional Therapy Group. *Hepatology* 1996;**24**:1034–40.

97. Saracco G, Rosina F, Torrani Cerenzia MR, Lattore V, Chiandussi L, Gallo V, *et al*. A randomized controlled trial of interferon alfa-2b as therapy for chronic non-A, non-B hepatitis. *J Hepatol* 1990;**11** (Suppl 1):S43–9.

98. Metreau JM. Results of long term interferon treatment in non A non B/C chronic active hepatitis. The French Group for the study of NANB/C chronic hepatitis treatment. *Gut* 1993;**34** (2 Suppl):S112–13.

99. Poynard T, Bedossa P, Chevallier M, Mathurin P, Lemonnier C, Trepo C, *et al*. A comparison of three interferon alfa-2b regimens for the long-term treatment of chronic non-A, non-B hepatitis. Multicenter Study Group. *N Engl J Med* 1995;**332**:1457–62.

100. Lin R, Roach E, Zimmerman M, Strasser S, Farrell GC. Interferon alfa-2b for chronic hepatitis C: effects of dose increment and duration of treatment on response rates. Results of the first multicentre Australian trial. Australia Hepatitis C Study Group. *J Hepatol* 1995;**23**:487–96.

101. Barbaro G, Di LG, Soldini M, Giancaspro G, Pellicelli A, Grisorio B, *et al*. Evaluation of long-term efficacy of interferon alpha-2b and ribavirin in combination in naive patients with chronic hepatitis C: an Italian multicenter experience. Ribavirin–Interferon in Chronic Hepatitis Italian Group Investigators. *J Hepatol* 2000;**33**:448–55.

102. Takahashi M, Yamada G, Miyamoto R, Doi T, Endo H, Tsuji T. Natural course of chronic hepatitis C. *Am J Gastroenterol* 1993;**88**:240–3.

103. Tremolada F, Casarin C, Alberti A, Drago C, Tagger A, Ribero ML, *et al*. Long-term follow-up of non-A, non-B (type C) post-transfusion hepatitis. *J Hepatol* 1992;**16**:273–81.

104. Mattsson L, Weiland O, Glaumann H. Long-term follow-up of chronic post-transfusion non-A, non-B hepatitis: clinical and histological outcome. *Liver* 1988;**8**:184–8.

105. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet* 1997;**349**:825–32.

106. Sobesky R, Mathurin P, Charlotte F, Moussalli J, Olivi M, Vidaud M, *et al*. Modeling the impact of interferon alfa treatment on liver fibrosis progression in chronic hepatitis C: a dynamic view. The Multivirc Group. *Gastroenterology* 1999;**116**:378–86.

107. Yano M, Yatsuhashi H, Inoue O, Inokuchi K, Koga M. Epidemiology and long term prognosis of hepatitis C virus infection in Japan. *Gut* 1993;**34** (2 Suppl):S13–16.

108. Shiratori Y, Imazeki F, Moriyama M, Yano M, Arakawa Y, Yokosuka O, *et al*. Histologic improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy. *Ann Intern Med* 2000;**132**:517–24.

109. Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Empirically calibrated model of hepatitis C virus infection in the United States. *Am J Epidemiol* 2002;**156**:761–73.

110. Dusheiko GM, Roberts JA. Treatment of chronic type B and C hepatitis with interferon alfa: an economic appraisal. *Hepatology* 1995;**22**:1863–73.

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

112. Sherman KE, Sherman SN, Chenier T, Tsevat J. Health values of patients with chronic hepatitis C infection. *Arch Intern Med* 2004;**164**:2371–82.

113. Krahn M, Ritvo P, Irvine J, Tomlinson G, Bezjak A, Trachtenberg J, *et al*. Construction of the Patient-Oriented Prostate Utility Scale (PORPUS): a multiattribute health state classification system for prostate cancer. *J Clin Epidemiol* 2000;**53**:920–30.

114. Bayliss MS, Gandek B, Bungay KM, Sugano D, Hsu MA, Ware JE Jr. A questionnaire to assess the generic and disease-specific health outcomes of patients with chronic hepatitis C. *Qual Life Res* 1998;**7**:39–55.

115. Pojoga C, Dumitrascu DL, Pascu O, Grigorescu M, Radu C, Damian D. Impaired health-related quality of life in Romanian patients with chronic

viral hepatitis before antiviral therapy. *Eur J Gastroenterol Hepatol* 2004;**16**:27–31.

116. Younossi ZM, Boparai N, Price LL, Kiwi ML, McCormick M, Guyatt G. Health-related quality of life in chronic liver disease: the impact of type and severity of disease. *Am J Gastroenterol* 2001;**96**:2199–205.

117. Wong JB, Bennett WG, Koff RS, Pauker SG. Pretreatment evaluation of chronic hepatitis C: risks, benefits, and costs. *JAMA* 1998;**280**:2088–93.

118. Dolan P, Gudex C, Kind P, Williams A. *A social tariff for EuroQol: results from a UK general population survey*. Centre for Health Economics. Discussion Paper 138. York: Centre for Health Economics, University of York; 1995.

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

120. Hui CK, Belaye T, Montegrande K, Wright TL. A comparison in the progression of liver fibrosis in chronic hepatitis C between persistently normal and elevated transaminase. *J Hepatol* 2003;**38**:511–17.

121. Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J. Pegylated interferon alpha-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess* 2004;**8**(39).

122. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. *J Hepatol* 1991;**13**:372–4.

123. Bruno S, Camma C, Di Marco V, Rumi M, Vinci M, Camozzi M, *et al*. Peginterferon alfa-2b plus ribavirin for naive patients with genotype 1 chronic hepatitis C: a randomized controlled trial. *J Hepatol* 2004;**41**:474–81.

124. Di Bisceglie AM, Thompson J, Smith-Wilkaitis N, Brunt EM, Bacon BR. Combination of interferon and ribavirin in chronic hepatitis C: re-treatment of nonresponders to interferon. *Hepatology* 2001;**33**:704–7.

125. National Institute for Clinical Excellence. *Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C*. URL: http://www.nice.org.uk/page.aspx?o=82254. 2004.

126. Siebert U, Sroczynski G, Rossol S, Wasem J, Ravens-Sieberer U, Kurth BM, *et al*. Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C. *Gut* 2003;**52**:425–32.

127. Roche UK. *Pegasys (peginterferon alfa-2a) NICE Submission – achieving clinical excellence in the treatment of mild chronic Hepatitis C*. Welwyn Garden City, Herts: Roche UK; 2005.

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

129. Longworth L, Young T, Ratcliffe J, Bryan S, Buxton M. *Economic evaluation of the Transplantation Programme in England and Wales: an assessment of the costs of liver transplantation*. Report to the Department of Health. 2001.

130. Curtis L, Netten A. *Unit costs of health and social care*. Canterbury: PSSRU, University of Kent; 2004.

131. Davis GL. Monitoring of viral levels during therapy of hepatitis C. *Hepatology* 2002;**36** (5 Suppl 1):S145–51.

132. Hopwood M, Southgate E. Living with hepatitis C: a sociological review. *Crit Public Health* 2003; **13**:251–67.

133. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A, *et al*. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004;**351**:438–50.

134. Mangia A, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, *et al*. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2005;**352**: 2609–17.

135. Zeuzem S, Pawlotsky JM, Lukasiewicz E, von Wagner M, Goulis I, Lurie Y, *et al*. International, multicenter, randomized, controlled study comparing dynamically individualized versus standard treatment in patients with chronic hepatitis C. *J Hepatol* 2005;**43**:250–7.

136. Wong JB, Poynard T, Ling MH, Albrecht JK, Pauker SG. Cost-effectiveness of 24 or 48 weeks of interferon alpha-2b alone or with ribavirin as initial treatment of chronic hepatitis C. International Hepatitis Interventional Therapy Group. *Am J Gastroenterol* 2000;**95**: 1524–30.

Appendix 1

Liver biopsy classification systems

Knodell (Histological Activity Index), 1981[22]

The Knodell score or histological activity index (HAI) is also commonly used to stage liver disease. It is a somewhat more complex process, but some experts believe that it is a better tool for defining the extent of liver inflammation and damage. It is composed of four individually assigned numbers that make up a single score:

1. Periportal and/or bridging necrosis is scored 0–10.
2. Intralobular degeneration is scored 0–4.
3. Portal inflammation is scored 0–4.
   (a) The combination of these three markers indicates the amount of inflammation in the liver:
      (i) 0 = no inflammation
      (ii) 1–4 = minimal inflammation
      (iii) 5–8 = mild inflammation
      (iv) 9–12 = moderate inflammation
      (v) 13–18 = marked inflammation.
4. The fourth component indicates the amount of scarring (fibrosis) in the liver and is scored from:
   (a) 0 (no scarring)
   (b) 1
   (c) 3
   (d) 4 (extensive scarring or cirrhosis).

The total possible HAI score is 22.

Ishak (Histological Activity Index), 1995[23]

This is a modified version of Knodell's system.

Modified HAI grading: necroinflammatory scores

Item	Score
A. Periportal or periseptal interface hepatitis (piecemeal necrosis)	
Absent	0
Mild (focal, few portal areas)	1
Mild/moderate (focal, most portal areas)	2
Moderate (continuous around 60% of tracts or septa)	3
Severe (continuous around >50% of tracts or septa)	4
B. Confluent necrosis	
Absent	0
Focal confluent necrosis	1
Zone 3 necrosis in some areas	2
Zone 3 necrosis in most areas	3
Zone 3 necrosis + occasional portal–central (P–C) bridging	4
Zone 3 necrosis + multiple P–C bridging	5
Panacinar or multiacinar necrosis	6
C. Focal (spotty) lytic necrosis, apoptosis and focal inflammation	
Absent	0
One focus or less per 10 × objective	1
Two to four foci per 10 × objective	2
Five to ten foci per 10 × objective	3
More than ten foci per 10 × objective	4
D. Portal inflammation	
None	0
Mild, some or all portal areas	1
Moderate, some or all portal areas	2
Moderate/marked, all portal areas	3
Marked, all portal areas	4
Maximum score for grading	18

Modified staging: architectural changes, fibrosis and cirrhosis

Change	Score
No fibrosis	0
Fibrous expansion of some portal areas, with or without short fibrous septa	1
Fibrous expansion of most portal areas, with or without short fibrous septa	2
Fibrous expansion of most portal areas with occasional portal to portal (P–P) bridging	3
Fibrous expansion of portal areas with marked bridging [P–P in addition to portal to central (P–C)]	4
Marked bridging (P–P and/or P–C) with occasional nodules (incomplete cirrhosis)	5
Cirrhosis, probable or definite	6
Maximum possible score	6

Disease severity thresholds

Fibrosis:

≤2 Mild
3–5 Moderate
6 Severe (cirrhosis)

Necro-inflammatory score:

1-8 Mild
9–18 Moderate/Severe

NB. If fibrosis = 6 then the patient is classified as having severe HCV, irrespective of the necro-inflammatory score.

Total Ishak HAI score = 24

METAVIR, 1996[24]

Specially designed for HCV

Necro-inflammation

A0 No histological activity
A1 Mild activity
A2 Moderate activity
A3 Severe activity

Fibrosis

F0 No scarring
F1 Minimal scarring
F2 Scarring has occurred but extends outside the areas that the liver contains blood vessels
F3 Bridging fibrosis is spreading and connecting to other areas that contain fibrosis
F4 Cirrhosis or advanced scarring of the liver

Total METAVIR score = 7

Appendix 2

Antiviral drugs: licensed indications

Interferon alfa-2a/2b

Interferon alfa has been used in the treatment of chronic hepatitis C for a number of years, primarily as a single agent, until the introduction of combination therapy with RBV in 1999. Interferons are naturally occurring proteins with complex effects on immunity and cell function, and there are at least 15 different molecular species. Interferon alfa was the first pure human protein found to be effective in the treatment of cancer and has been used to treat chronic myelogenous leukaemia and other myeloproliferative disorders, renal carcinoma and infections such as chronic hepatitis B.

Three preparations are available:

- interferon alfa-2a (Roferon A, Roche)
- interferon alfa-2b (Intron A, Schering-Plough)
- interferon alfa-2b (Viraferon, Schering-Plough).

Pegylated interferon alfa-2a/2b

A newer 'pegylated' derivative of interferon alfa has superseded the use of 'conventional' non-pegylated interferon. Pegylation involves the attachment of an inert polyethylene glycol polymer to the interferon molecule to produce a larger molecule with a prolonged half-life. Pegylation prolongs the biological effect necessitating fewer injections and therefore is more convenient for patients. There are differences between the two pegylated interferons, such as the size and structure of their polyethylene glycol molecule and the bond between the PEG molecule and the interferon.

The pegylated interferons are licensed in Europe for the treatment of chronic hepatitis C in combination with RBV (or as monotherapy in those for whom RBV is contraindicated) (pegylated interferon alfa-2a is also licensed in the EU for the treatment of chronic hepatitis B). Treatment is indicated in both previously untreated patients, and for those who have previously been treated with, and responded to, interferon alfa but who have subsequently relapsed.

Three preparations are available:

- 40-kDa pegylated interferon alfa-2a (Pegasys; Roche). Currently indicated for the treatment of chronic hepatitis C in adult patients who are positive for serum HCV RNA, including patients with compensated cirrhosis. A licence variation was announced in 2003 to remove the phrase 'histologically proven' for patients with genotypes 2 and 3. Further, the European Medicines Agency (EMEA) announced in November 2004 that it had approved Pegasys for the treatment of chronic hepatitis C patients with persistently normal liver enzymes (it had previously been indicated in patients with elevated ALT levels).
  Dose: 180 μg/week via subcutaneous injection.
- 12-kDa pegylated interferon alfa-2b (PegIntron, Schering-Plough). Currently indicated for the treatment of adult patients who have elevated transaminases without liver decompensation and who are positive for serum HCV RNA or anti-HCV.
  Dose: 1.5 μg/kg/week via subcutaneous injection.
- 12-kDa pegylated interferon alfa-2b (ViraferonPeg; Schering-Plough). Licensed indication as for PegIntron.

Ribavirin

RBV is a synthetic nucleoside analogue with a broad spectrum of antiviral activity against DNA and RNA viruses. It is indicated in combination with PEG or IFN for patients with chronic hepatitis C not previously treated, without liver decompensation and who have fibrosis or high inflammatory activity or for relapse following previous response to IFN.

Two preparations are available for use in chronic hepatitis C:

- Rebetol, Schering-Plough.
  Dose: body-weight <65 kg, 400 mg twice daily; body weight 65–85 kg, 400 mg in the morning and 600 mg in the evening; body weight >85 kg, 600 mg twice daily.
- Copegus, Roche.

Dose: body weight <75 kg, 400 mg in the morning and 600 mg in the evening; body weight ≥75 kg, 600 mg twice daily. For patients with genotypes 2 or 3, the dose of Copegus is lower (800 mg), usually administered as 400 mg twice daily.

Appendix 3

Clinical-effectiveness search strategy (MEDLINE, via Ovid)

1 (hepatitis c or HCV).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2 exp Hepatitis C/
3 Hepatitis C, Chronic/
4 Hepacivirus/
5 1 or 2 or 3 or 4
6 (peginterferon$ or peg-ifn or peg-interferon$ or (pegylat$ adj3 interferon$) or peg$ or (polyethylene glycol adj3 interferon$) or ViraferonPeg or pegintron or Pegasys).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7 5 and 6
8 limit 7 to (english language and yr=2003-2005)
9 exp interferon type i, recombinant/ or exp interferon-alpha/ or exp interferon alfa-2a/ or exp interferon alfa-2b/ or exp interferon alfa-2c/
10 (interferon alpha or interferon alfa or roferon or intron or viraferon).ti,ab.
11 9 or 10
12 11 and 5
13 limit 12 to (english language and yr=2000-2005)
14 13 not 8
15 meta-analysis/
16 (meta analysis or metaanalysis).ab,pt,ti.
17 (systematic$ adj2 (review$ or overview$)).ti,ab,pt.
18 or/15-17
19 (letter or editorial or comment).pt.
20 18 not 19
21 randomized controlled trial.pt.
22 controlled clinical trial.pt.
23 randomized controlled trials/
24 random allocation/
25 double-blind method/
26 single-blind method/
27 exp evaluation studies/
28 exp clinical trials/
29 clinical trial.pt.
30 (clin$ adj5 trial$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
31 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
33 exp placebos/
34 placebo$.tw.
35 random$.tw.
36 exp research design/
37 32 or 33 or 34 or 35 or 36
38 31 or 37
39 8 and 20
40 8 and 38
41 14 and 20
42 14 and 38

The clinical effectiveness search strategy was combined with a systematic review and RCT filter where possible to locate high-quality evidence.

The above strategy was translated to run in the following electronic databases: MEDLINE (Ovid); PreMEDLINe (Ovid); EMBASE (Ovid); Cochrane Library including Cochrane Database of Systematic Reviews; Cochrane CENTRAL Register of Controlled Trials; Centre for Reviews and Dissemination (University of York) databases: DARE (Database of Abstracts of Reviews of Effects) HTA (Health Technology Assessment Database); ISI Web of Science, Science Citation Index, ISI Proceedings; BIOSIS Previews (Edina); National Research Register; Current Controlled Trials; Clinical Trials.

Appendix 4

Costs and cost-effectiveness search strategy

The cost-effectiveness searches were run in MEDLINE (Ovid), EMBASE (Ovid), CRD NHS EED (Economic Evaluations Database) and EconLit.

MEDLINE, via Ovid

1 (hepatitis C or hcv).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2 exp Hepatitis C/ or Hepatitis C, Chronic/ or exp Hepacivirus/
3 or/1-2
4 exp "costs and cost analysis"/
5 Cost-Benefit Analysis/
6 exp Health Care Costs/
7 4 or 5 or 6
8 7 and 3
9 limit 8 to (english language and yr=2000 - 2005)

EMBASE, via Ovid

1 (hepatitis C or hcv).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
2 exp Hepatitis C/ or exp Hepatitis C virus/
3 or/1-2
4 (peginterferon$ or peg-ifn or peg-interferon$ or (peg$ adj3 interferon$) or (polyethylene glycol adj3 interferon$) or Pegasys or pegintron or viraferonpeg).mp.
5 peginterferon/ or peginterferon alpha2a/ or peginterferon alpha2b/
6 4 or 5
7 3 and 6
8 limit 7 to (english language and yr=2003-2005)
9 interferon/ or alpha2a interferon/ or alpha2b interferon/ or alpha interferon/
10 (interferon alpha or interferon alfa or roferon or intron or viraferon).ti,ab.
11 9 or 10
12 3 and 11
13 12 not 7 (
14 limit 13 to (english language and yr=2000-2005)
15 (cost$ adj2 effective$).ti,ab.
16 (cost$ adj2 benefit$).ti,ab.
17 cost effectiveness analysis/
18 cost benefit analysis/
19 budget$.ti,ab.
20 cost$.ti.
21 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
22 (economic$ or pharmacoeconomic$ or pharmaco economic$).ti.
23 (price$ or pricing$).ti,ab.
24 (financial or finance or finances or financed).ti,ab.
25 (fee or fees).ti,ab.
26 cost/
27 cost minimization analysis/
28 cost of illness/
29 cost utility analysis/
30 drug cost/
31 health care cost/
32 health economics/
33 economic evaluation/
34 economics/
35 pharmacoeconomics/
36 budget/
37 economic burden.ti,ab.
38 "resource use".ti,ab.
39 or/15-38
40 (editorial or letter).pt.
41 39 not 40
42 41 and 3
43 41 and 8
44 41 and 14

Appendix 5

Health-related quality of life search strategy

The HRQoL search strategy was translated and applied to MEDLINE, PreMEDLINE and EMBASE (Ovid).

MEDLINE, via Ovid

1 value of life/
2 quality adjusted life year/
3 quality adjusted life.ti,ab.
4 (qaly$ or qald$ or qale$ or qtime$).ti,ab.
5 disability adjusted life.ti,ab.
6 daly$.ti,ab.
7 health status indicators/
8 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.
9 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.
10 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab.
11 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.
12 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab.
13 (euroqol or euro qol or eq5d or eq 5d).ti,ab.
14 (hql or hqol or h qol or hrqol or hr qol).ti,ab.
15 (hye or hyes).ti,ab.
16 health$ year$ equivalent$.ti,ab.
17 health utilit$.ab.
18 (hui or hui1 or hui2 or hui3).ti,ab.
19 disutil$.ti,ab.
20 rosser.ti,ab.
21 quality of well being.ti,ab.
22 quality of wellbeing.ti,ab.
23 qwb.ti,ab.
24 willingness to pay.ti,ab.
25 standard gamble$.ti,ab.
26 time trade off.ti,ab.
27 time tradeoff.ti,ab.
28 tto.ti,ab.
29 (index adj2 well being).mp.
30 (quality adj2 well being).mp.
31 (health adj3 utilit$ ind$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
32 ((multiattribute$ or multi attribute$) adj3 (health ind$ or theor$ or health state$ or utilit$ or analys$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
33 quality adjusted life year$.mp.
34 (15D or 15 dimension$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
35 (12D or 12 dimension$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
36 rating scale$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
37 linear scal$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
38 linear analog$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
39 visual analog$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
40 (categor$ adj2 scal$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
41 or/1-40 (
42 (letter or editorial or comment).pt.
43 41 not 42
44 (hepatitis C or hcv).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
45 exp Hepatitis C/ or Hepatitis C, Chronic/ or exp Hepacivirus/
46 44 or 45
47 46 and 43
48 limit 47 to (english language and yr=2000 - 2005)

Appendix 6

Epidemiology search strategies (MEDLINE, via Ovid)

The epidemiology/ natural history searches were run in MEDLINE, PreMEDLINE and EMBASE (Ovid) databases.

1 (hepatitis C or hcv).mp.
2 exp Hepatitis C/ or Hepatitis C, Chronic/ or exp Hepacivirus/
3 or/1-2
4 incidence.ti.
5 prevalence.ti.
6 epidemiol$.ti.
7 ((natural$ or disease$ or fibrosis or cirrhosis or hepatocellular carcinoma) adj4 (progress$ or course$ or histor$ or survival)).ti,ab.
8 Alanine Transaminase/bl
9 (normal adj4 (aminotransferase or transaminase)).mp.
10 or/4-9
11 3 and 10
12 limit 11 to (english language and yr=2003 - 2005)

Appendix 7

Inclusion worksheet for clinical effectiveness studies

Trial Name or Number:				
Patients with **mild chronic Hepatitis C***? Mild HCV defined by liver biopsy fibrosis threshold scores • Ishak ≤2/6 • Knodell ≤1/4 • METAVIR ≤1/5 • Scheur ≤1/4 • or other scoring/staging systems • Proportion of patients below the threshold in trial at baseline, if reported, should be no less than 70% • Mean/median score (if reported) should be lower than the 70% threshold • However, trial can be included if SVR is reported for sub-group of mild patients	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	Type: EXCLUDE1 (not HCV or mild HCV)
Design: RCT or systematic review***	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	EXCLUDE2 (not the right study design)
Intervention** 1. Pegylated interferon + ribavirin 2. Pegylated interferon monotherapy 3. Interferon (non-pegylated) + ribavirin Report one or more of **primary outcomes**: sustained clearance of infection (absence of viral RNA 6 months or longer after end of treatment); adverse effects; quality of life; long-term complications avoided	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	EXCLUDE3 (not the right intervention) EXCLUDE4 (not the right outcome measures)
Final Decision	**INCLUDE**	**UNCLEAR (Discuss)**	**EXCLUDE**	**Results of Discussion:**

*NB. It is unlikely that many studies will report disease severity in title and abstract so advice is to be over-inclusive at this stage and include any relevant study that includes patients with HCV. Obvious exceptions include where the patients have cirrhosis, decompensated liver disease, hepatocellular carcinoma or are undergoing liver transplant. These patients, by definition, have moderate to severe disease.

**Likely comparators (can include, but not restricted to):

1) PEG + RBV vs:
   - PEG + RBV (different dose/regimen or in different patient subgroup)
   - No treatment
   - IFN + RBV
   - PEG monotherapy
   - IFN monotherapy

2) PEG monotherapy vs:
   - PEG monotherapy (different dose/regimen or in different patient subgroup)
   - No treatment
   - IFN monotherapy

3) IFN + RBV vs:
   - IFN + RBV (different dose/regimen or in different patient subgroup)
   - No treatment
   - IFN monotherapy

*** Systematic review normally defined by reporting of search strategy and inclusion criteria. Not all systematic reviews report an explicit assessment of quality but if reported this is an additional indicator that the review has been conducted according to 'systematic' methods.

Appendix 8

Cheng and colleagues:[67] data extraction and critical appraisal

Reference and design	Intervention	Participants	Outcome measures
Cheng *et al.*, 2002[67] **Trial design:** Double-blind RCT **Country:** Taiwan **Sponsor:** Schering-Plough AB and National Cheng-Kung University Hospital, Taiwan	**Intervention 1:** *n* = 26 IFN 2b (s.c.): Dose: 6 MU 3 times per week Duration: 24 weeks RBV (oral): Dose: twice daily at a total dose of 1000 mg for patients ≤75 kg, 1200 mg for patients >75 kg Duration: 24 weeks **Intervention 2:** *n* = 26 IFN 2b (s.c.): Dose: 6 MU 3 times per week Duration: 24 weeks Placebo Dose: twice daily Duration: 24 weeks	**Total numbers involved:** 72 screened, 52 randomised and analysed **Eligibility:** adult chronic HCV patients who had previously responded to IFN but who had then relapsed, positive HCV antibody, HCV RNA positive, using effective contraception **Recruitment:** patients from the National Cheng-Kung Hospital, Taiwan, between January 1999 and July 2000 **Exclusion criteria:** patients aged <18 or >65 years, decompensated liver disease, other causes of chronic liver disease (hepatitis B, Epstein–Barr virus, cytomegalovirus, autoimmune hepatitis and metabolic liver diseases), haemoglobin <13 mg/dl for males or <12 mg/dl for females, white blood cell count <4000/mm^3, neutrophil count <2000/mm^3, platelet count <100,000/mm^3, chronic alcoholism, HIV infection, pregnancy, previous organ transplant, severe psychiatric conditions, seizure disorders, renal failure, evidence of ischaemic heart disease, retinal abnormalities, poorly controlled diabetes mellitus, haemoglobinopathy, haemophilia **Baseline measurements:** **Viral load,** mean HCV RNA (± SD), MEq/ml: 6.7 (± 9.9) Group 1, 8.2 (± 12.7) Group 2 **Serum ALT**, mean (± SD), U/l: 206.2 (± 175.0) Group 1, 229.0 (± 195.6) Group 2 **Histology:** Classification system used: Knodell Fibrosis score, mean (± SD): 0.5 (±1.0) Group 1, 0.2 (± 0.4) Group 2 Necro-inflammatory score, mean (± SD): 2.1 (± 1.3) Group 1, 2.2 (± 1.8) Group 2 Timing of liver biopsy: performed before and at the end of treatment **Genotypes, no. (%):** 1b: 22 (42%) 2a + c: 22 (42%) 2b: 2 (4%) 1a + 2: 3 (6%) 2 (not subtyped): 3 (6%)	**Primary outcomes:** SVR (loss of detectable serum HCV RNA at end of follow-up) **Secondary outcomes:** • end of treatment virological response • biochemical response (normalisation of ALT[a]) • change in liver histology • adverse events **Length of follow-up:** 24 weeks after stopping treatment

continued

Reference and design	Intervention	Participants	Outcome measures
		Gender, no. (%): 41 male (79%), 11 female (21%) **Age (year), mean (± SD):** 43.4 (± 10.3) Group 1; 45.1 (± 8.5) Group 2 **Ethnic groups, no. (%):** not reported **Mode of infection, no. (%):** not reported **Losses to follow-up:** 0 **Compliance:** 2 patients did not complete the study: 1 withdrew due to adverse effects, 1 was withdrawn due to decreased neutrophil count	

Outcome % (no.)	IFN 2b (6 MU) + RBV (100–1200 mg)	IFN 2b (6 MU) + placebo	*p*-Value (between-group comparison)
Viral response:			
End of treatment	92% (24/26)	81% (21/26)	NS
SVR at follow-up	69% (18/26)	23% (6/26)	<0.001
SVR by genotype:			
1	50% (7/14)	27% (3/11)	
Non-1	92% (11/12)[b]	20% (3/15)	<0.005
SVR by viral load:			
≤3 MEq/ml	92% (12/13)[c]	50% (6/12)[d]	<0.05
>3 MEq/ml	46% (6/13)	0 (0/14)	<0.005
Biochemical response:			
End of treatment	92% (24/26)	81% (21/26)	NS
End of follow-up	65% (17/26)	19% (5/26)	<0.001
Histological improvement (n = 48):			
Inflammation, mean decrease	1.3 ± 0.5	1.3 ± 0.5	
Fibrosis, mean decrease	0.8 ± 3.3	0.0 ± 2.1	0.27
Adverse events,[e] no. (%):			
Dose discontinuation for			
Adverse event	1 (4)	0 (0)	
Other[f]	1 (4)	0 (0)	
Dose reduction for:			
Anaemia	6 (23)	0 (0)	
Other[g]	6 (23)	8 (31)	
Specific adverse events			
Malaise	22 (84)	20 (76)	
Fever	20 (76)	19 (73)	
Headache	19 (73)	18 (69)	
Rigors	14 (53)	12 (46)	
Anorexia	23 (88)	17 (65)	<0.05
Diarrhoea	10 (38)	7 (26)	
Insomnia	18 (69)	10 (38)	<0.05
Depressed mood	4 (15)	3 (11)	
Alopecia	19 (73)	19 (73)	
Palpitation	4 (15)	2 (7)	
Cough	4 (15)	3 (11)	

[a] Normal range of ALT values is within 5–55 U/l.
[b] $p < 0.05$ for comparison with genotype 1.
[c] $p < 0.05$ for comparison with HCV RNA level >3 MEq/ml.
[d] $p < 0.005$ for comparison with HCV RNA level >3 MEq/ml.
[e] Only adverse events that occurred >5% were included.
[f] Decreased neutrophil count.
[g] Leucopenia or neutropenia.

Additional results:
Histological response:
- In non-responders, a decrease in the inflammation score (1.00 ± 2.04), but not a decrease in the fibrosis score (–0.29 ± 1.27), was observed.

Predictive values of response:
- In week 4, the IFN + placebo group reached 83% sensitivity, 45% specificity, 31% PPV and 90% NPV. In comparison, the IFN + RBV group reached 90% sensitivity, 100% specificity, 90% PPV and 100% NPV (for definitions, see below).

Safety:
- Haemoglobin values were significantly lower in the IFN–RBV group than in the IFN–placebo group after the second week of treatment. However, haemoglobin values returned to baseline values within 4 weeks after completion of treatment.

Methodological comments:
Allocation to treatment groups: patients were randomly assigned to one of two treatment arms by the random permuted block method. Does not state whether this is computer generated or manual.
Allocation concealment: random permuted block method – reference cited.
Blinding of outcome assessors: study described as double-blind. Patients received RBV or a matched placebo. All biochemical and haematological tests were performed by autoanalysers – no further details. An experienced pathologist who was unaware of treatment aims and results analysed liver biopsy samples.
Analysis by ITT: reports that data were analysed by ITT. Results were reported for all 52 randomised patients.
Comparability of treatment groups at pretreatment: groups appear comparable at baseline for demographic, biochemical, haematological and histological characteristics. Statistical values not presented.
Method of data analysis: Statistical methods used to analyse the data included χ^2 test, Fisher's exact test and Student's *t*-test with a Type I error of 0.05, two-tailed as appropriate.
Power analysis: to detect a 35% difference in the rate of primary end-point between IFN and IFN–RBV treatments, with a power of 80% and a two-tailed Type I error of 0.05; 19 patients on each treatment were needed.
Attrition/drop-out: Two patients in the IFN–RBV group (2/26, 8%) did not complete the study. One patient withdrew due to insomnia, palpitation and dizziness at week 3 of treatment; the other was withdrawn at week 8 of treatment due to decreased neutrophil count. Pre- and post-treatment liver biopsies were collected from 48 of 52 patients – 2 patients refused biopsy, in 2 patients only pretreatment biopsy specimens were collected due to withdrawal from study.

General comments
Generalisability: Patients with mild chronic HCV without other co-morbidities – mean fibrosis is very low (≤0.5). The authors report that patients represented a reasonable genotypic cross-section of the contemporary Taiwanese population.
Conflict of interests: Study supported in part by a grant from Schering-Plough AB.
Other: The paper states that the decreased fibrosis score for the IFN/RBV group was 0.8 ± 3.3. However, baseline mean fibrosis score for this group was 0.5 ± 1.0. Therefore, it is assumed that this is 0.8 of 0.5 = 0.4.
Definitions: Sensitivity, fraction of all SVR patients identified by undetectable HCV RNA; specificity, fraction of all non-SVR patients identified by detectable HCV RNA; PPV, positive predictive value, chance of SVR if HCV RNA is undetectable; NPV, negative predictive value, chance of non-SVR if HCV RNA is detectable; Knodell histological activity index inflammation score ranged from 0 to 18; histological improvement was defined as a decrease in the inflammation score of at least two points or a decrease in the fibrosis score of at least one point relative to the pretreatment biopsy.

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Partial
2. Was the treatment allocation concealed?	Inadequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Inadequate
6. Was the patient blinded?	Partial
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
8. Did the analysis include an ITT analysis?	Adequate
9. Were losses to follow-up completely described?	Adequate

Appendix 9

Chung and colleagues:[68] data extraction and critical appraisal

Reference and design	Intervention	Participants	Outcome measures
Chung *et al.*, 2004[68] **Trial design:** Multicentre RCT **Country:** USA **Sponsor:** National Institutes of Health	**Intervention 1:** *n* = 66 PEG 2a (s.c.): Dose: 180 μg once weekly Duration: 48 weeks RBV (oral): Dose: 600 mg daily Duration: 4 weeks Dose: 800 mg daily Duration: 4 weeks Dose: 1000 mg daily Duration: 40 weeks **Intervention 2:** *n* = 67 IFN 2a (s.c.): Dose: 6 million IU three times per week Duration: 12 weeks Dose: 3 MU three times per week Duration: 36 weeks RBV (oral): Dose: 600mg daily Duration: 4 weeks Dose: 800 mg daily Duration: 4 weeks Dose: 1000 mg daily Duration: 40 weeks	**Total numbers involved:** 133 randomised and analysed **Eligibility:** HIV-infected patients, aged ≥ 18 years, confirmed diagnosis of chronic hepatitis C (>600 IU/ml HCV RNA level), biopsy findings consistent with the presence of chronic hepatitis C, not previously treated with IFN, normal or elevated ALT levels, cirrhosis acceptable provided there was no evidence of hepatic decompensation (i.e. ascites, encephalopathy, jaundice, hypoalbuminaemia or coagulopathy) **Recruitment:** 21 centres in the USA between December 2000 and June 2001 **Exclusion criteria:** clinically significant anaemia, neutropenia or thrombocytopenia; renal disease; positive tests for hepatitis B surface antigen; uncontrolled cardiopulmonary disease; poorly controlled psychiatric disease; active HIV-related opportunistic infection **Baseline measurements:** **Viral load**, HCV RNA level × 10^{-6} IU/ml Mean (± SD): 6.2 (± 0.4) Group 1, 6.2 (± 0.3) Group 2 >1 × 10^{6} IU/ml, %: 83% Group 1, 82% Group 2 **ALT,** abnormal level, %: 66% Group 1, 68% Group 2 **Histology:** Classification system used: Ishak Fibrosis score, median: 2.0 Group 1, 2.0 Group 2 Cirrhosis, %: 11% Group 1, 9% Group 2 Hepatitis activity index score, median: 5.0 Group 1, 5.0 Group 2 Timing of liver biopsy: within 48 weeks before study entry **Genotype 1**, %: 77% Group 1, 78% Group 1 **Gender, no**. (%): 109 male (82%), 24 female (18%) **Age, mean:** 45 years Group 1, 44 years Group 2	**Primary outcomes:** Virological response at week 24 of treatment **Secondary outcomes:** • SVR • end of treatment virological response • early virological response • histological response • adverse events **Length of follow-up:** 24 weeks after completion of therapy

continued

Reference and design	Intervention	Participants	Outcome measures
		Ethnic groups, no. (%): White: 64 (48%) Black: 44 (33%) Hispanic: 18 (14%) Other: 7 (5%) **Mode of infection, no. (%):** not reported **Losses to follow up:** 8 subjects in each group (12%) were prematurely withdrawn from treatment because of abnormalities in laboratory values or adverse events **Compliance:** 0	

Outcome, no. (%)	PEG 2a + RBV	IFN 2a + RBV	*p*-Value (between-group comparison)
Viral response:			
24 weeks	29/66 (44%)	10/67 (15%)	<0.001
End of treatment (48 weeks)	27/66 (41%)	8/67 (12%)	<0.001
SVR at follow-up	18/66 (27%)	8/67 (12%)	0.03
SVR by genotype:			
1	7/51 (14%)	3/52 (6%)	
Non-1	11/15 (73%)[a]	5/15 (33%)[a]	0.07
Histology			
No virological response at week 24:	(*n* = 37)	(*n* = 57)	
Histological response	9/26[b] (35%)	16/45[c] (36%)	
Virological response at week 24:	(*n* = 39)		
Histological improvement	14/27[d] (52%)		
No change	11/27[d] (41%)		
Worsening disease	2/27[d] (7%)		
Adverse events at weeks 0–24, no. of subjects[e]:	(*n* = 66) Grade 2/3/4[f]	(*n* = 67) Grade 2/3/4[f]	
Signs and symptoms	26/15/0	20/19/1	
Influenza-like symptoms	19/12/0	20/13/0	
Depression	5/2/0	6/2/0	
Abnormal laboratory values	18/22/15	26/21/4	
Anaemia	0/0/2	1/0/0	
Neutropenia	13/18/5	10/7/3	
Thrombocytopenia	10/2/1	2/0/0	
Glucose high or low	12/3/4	14/2/0	
ALT high	18/2/0	12/7/0	
Lipase high	5/4/0	6/3/0	
Lactate high	0/0/0	0/1/0	
Adverse events at weeks 25–72, no. of subjects[e]:	(*n* = 35) Grade 2/3/4[f]	(*n* = 26)[g] Grade 2/3/4[f]	
Signs and symptoms	10/4/0	7/3/0	
Influenza-like symptoms	5/3/0	4/1/0	
Depression	1/1/0	0/0/0	
Abnormal laboratory values	13/10/7	8/4/1	
Anaemia	0/0/1	0/0/0	
Neutropenia	7/6/4	1/2/0	
Thrombocytopenia	3/0/0	0/0/0	
Glucose high or low	5/4/1	4/1/0	
ALT high	5/2/0	1/0/1	
Lipase high	3/1/0	2/1/0	
Lactate high	0/0/0	0/0/0	
Dose discontinuation	8	8	

continued

Outcome, no. (%)	PEG 2a + RBV	IFN 2a + RBV	*p*-Value (between group comparison)

[a] $p < 0.001$ for comparison with genotype 1.
[b] 26 of 37 subjects underwent liver biopsy.
[c] 45 of 57 subjects underwent liver biopsy.
[d] 27 of 39 subjects underwent liver biopsy at week 48.
[e] Subjects could have >1 adverse event.
[f] Grade 2 indicates a moderate adverse event, grade 3 a severe adverse event, grade 4 a potentially life-threatening adverse event.
[g] Included 3 subjects who continued treatment beyond week 24 while awaiting liver biopsy.

Additional results:

Virological response:

- In genotype 1 subjects at week 24, the virological response was 33% (17/51) and 8% (4/52) for PEG and IFN, respectively ($p = 0.001$); in genotype non-1 (predominantly genotypes 2 and 3), the virological response was 80% (12/15) and 40% (6/15) for PEG and IFN, respectively.
- In genotype 1 subjects at the end of treatment, the virological response was 29% (15/51) and 6% (3/52) for PEG and IFN, respectively; in genotype non-1, the virological response was 80% (12/15) and 33% (5/15) for PEG and IFN, respectively ($p < 0.001$ for genotype non-1 vs genotype 1 for the PEG group).
- Receipt of PEG + RBV, genotype non-1, absence of prior injection drug use, a detectable level of HIV-1 RNA at entry, and a Karnofsky score of 100 were predictive of an SVR in univariate analysis. In multivariate analysis, all these variables except the Karnofsky score independently predicted an SVR.
- Of the 106 subjects in whom HCV RNA levels were measured at week 12, 43 (41%) had an early virological response; 22 of these 43 subjects (51%) had an SVR. In contrast, none of the 63 subjects who did not have an early virological response had an SVR (negative predictive value, 100%).

Safety:

- The rate of premature withdrawal (12%) was similar to that in similar studies of subjects with HCV monoinfection. Also, see *Attrition/drop-out* below.
- 2 subjects in the PEG group discontinued therapy because of grade 4 neutropenia (<500 neutrophils/mm^3). In 6 others (3 PEG, 3 IFN), grade 4 neutropenia was successfully managed with a dose reduction, with or without haematopoietic growth factor.
- There was one hospitalisation due to clinically significant pancreatitis, and treatment was discontinued at week 16. The subject was also receiving didanosine. Of 18 subjects with lipase elevations of grade 2 or higher, 4 were taking didanosine.

Methodological comments:

Allocation to treatment groups: randomisation was stratified according to HCV genotype (1 vs non-1) and antiretroviral therapy status (current vs none). No details reported on actual randomisation method.
Allocation concealment: not reported.
Blinding of outcome assessors: a central pathologist assessed histologic response; no further details reported.
Analysis by ITT: reports that data were assessed using ITT analysis. Results were reported for all 133 randomised patients.
Comparability of treatment groups at pretreatment: there were no statistically significant differences between groups at baseline for demographics, histology, biochemical or HIV-related characteristics.
Method of data analysis: Associations between dichotomous variables were evaluated with Fisher's exact test. Associations involving ordered categorical data or continuous data were evaluated with a Wilcoxon test adjusted for ties. Univariate- and multicovariate-adjusted *p*-values for the association of the virological response at week 24 with covariates were evaluated with logistic regression stratified according to the HCV genotype and HIV treatment history. All *p*-values were two-sided. Univariate analyses of SVR were performed with log-rank tests and multicovariate analyses with proportional hazards regression. Because of the limited sample size and because SVR was not a primary outcome, these tests were not stratified according to the group or the HCV genotype. The proportion of subjects who continued to have SVR was estimated with the use of the life-table method.
Power analysis: the study was designed to have a statistical power of 80% (with a two-sided α value of 0.05) to detect an absolute difference in the rate of virological response between groups of 30%. The target sample size of 132 was adjusted for a group-sequential design.
Attrition/drop-out: 8 subjects in each group (12%) were prematurely withdrawn from treatment because of abnormalities in laboratory values or other adverse events. Of the 16 subjects, 3 declined further participation and 1 died of unrelated causes. The remaining 12 were withdrawn because of neuropsychiatric issues (primarily depression) or the need to manage multiple signs and symptoms and abnormal lab values.

continued

General comments
Generalisability: subjects were co-infected with HIV.
Conflict of interests: six authors reported having received consulting fees or grant support from a range of pharmaceutical companies; 3 of these authors received fees/support from Roche and Schering-Plough.
Other: study design – treatment duration was 48 weeks. However, an efficacy and safety assessment was performed at week 24 to determine whether subjects could continue. Subjects who had a virological response continued treatment until week 48, at which time they had a liver biopsy. Subjects with no virological response at week 24 underwent a liver biopsy at that time. Those with a histological response continued treatment until week 48; those with no histological response or who did not undergo biopsy stopped taking the study drug.
Definitions: SVR, HCV RNA level <60 IU/ml 24 weeks after completion of therapy, allowing a 6-week window for the sample; end of treatment response, HCV RNA level <60 IU/ml at the completion of therapy; early virological response, the clearance of HCV RNA or a reduction in HCV RNA levels by more than 2 log (on a base-10 scale) IU/ml at 12 weeks of treatment; histological response, an improvement in the total hepatic activity index of at least two points as judged by a pathologist.

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the patient blinded?	Not applicable as trial was open-label
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
8. Did the analysis include an ITT analysis?	Adequate
9. Were losses to follow-up completely described?	Adequate

Appendix 10

Hadziyannis and colleagues:[69] data extraction and critical appraisal

Reference and design	Intervention[a]	Participants	Outcome measures
Hadziyannis *et al.*, 2004[69] **Trial design:** Multicentre, double-blind RCT **Country:** International **Sponsor:** Roche	**Intervention 1: 24-LD** *n* = 207 PEG 2a: Dose: 180 μg/week Duration: 24 weeks RBV: Dose: 800 mg/day Duration: 24 weeks **Intervention 2: 24-SD** *n* = 280 PEG 2a: Dose: 180 μg/week Duration: 24 weeks RBV: Dose: 1000 mg/day for patients <75 kg, 1200 mg/day for patients ≥75 kg Duration: 24 weeks **Intervention 3: 48-LD** *n* = 361 PEG 2a Dose: 180 μg/week Duration: 48 weeks RBV: Dose: 800 mg/day Duration: 48 weeks **Intervention 4: 48-SD** *n* = 436 PEG 2a: Dose: 180 μg/week Duration: 48 weeks RBV: Dose: 1000 mg/day for patients <75 kg, 1200 mg/day for patients ≥75 kg Duration: 48 weeks	**Total numbers involved:** 1736 screened, 1311 randomised, 1284 analysed **Eligibility:** treatment-naïve adult patients, serum HCV RNA >2000 copies/ml, elevated serum ALT (documented on ≥2 occasions ≥14 days apart within previous 6 months), compensated liver disease, biopsy consistent with CHC (obtained in previous 15 months) **Recruitment:** 99 centres in Europe, North and South America, Australia, New Zealand and Taiwan, between November 1999 and January 2002 **Exclusion criteria:** neutropenia (neutrophil count $<1.5 \times 10^9$ cells/l), thrombocytopenia (platelet count $<90 \times 10^9$ cells/l), anaemia (haemoglobin level <120 g/l in women and <130 g/l in men) or a medical condition that would be clinically significantly worsened by anaemia, serum creatinine level >1.5 times the upper limit of normal, co-infection with hepatitis A or B virus or HIV, history of bleeding from oesophageal varices or other conditions consistent with decompensated liver disease, organ transplant, severe or poorly controlled psychiatric disease (especially depression), malignant neoplastic disease, severe cardiac or chronic pulmonary disease, immunologically mediated disease (except controlled thyroid disease), seizure disorder, severe retinopathy, alcohol or drug dependence within 1 year of study entry, clinically significant co-morbid medical conditions, pregnancy, unwillingness to practise contraception **Baseline measurements:** **Viral load**, mean HCV RNA level $\times 10^3$ copies/ml (± SD): 5047 (± 5358) 24-LD 5513 (± 7002) 24-SD 7156 (± 8223) 48-LD 6059 (± 6847) 48-SD Mean ALT, U/l:[b] 88.3 (± 62.5) 24-LD 91.1 (± 67.5) 24-SD 81.3 (± 52.6) 48-LD 87.0 (± 60.9) 48-SD	**Primary outcomes:** SVR **Secondary outcomes:** • end of treatment virological response • adverse events **Length of follow-up:** 24 weeks after completion of treatment

continued

Reference and design	Intervention[a]	Participants	Outcome measures
		Histology: Classification system used: Knodell Fibrosis score, no. (%): Non-cirrhosis (F0, F1): 963 (75%) Bridging cirrhosis (F3): 231 (18%) Cirrhosis (F4): 90 (7%) Timing of liver biopsy: obtained within previous 15 months **Genotypes, no. (%):** 1: 740 (58%) Non-1: 544 (42%) 2: 204 (16%) 3: 288 (22%) **Gender, no. (%):** 838 male (65%), female 446 (35%) **Age (years), mean (± SD):** 41.2 (± 8.9) 24-LD 42.0 (± 9.2) 24-SD 42.6 (± 10.4) 48-LD 43.0 (± 10.1) 48-SD **Ethnic groups, no. (%):** White: 1146 (89%) Black: 38 (3%) Asian: 87 (7%) Other: 13 (1%) **Mode of infection, no. (%):**[c] Injection drug use: 457 (36%) Transfusion: 231 (18%) Unknown or other: 427 (33%) **Losses to follow up:** 270 patients discontinued treatment (of whom 18 were lost to follow-up). 1014 patients completed their allocated treatment, which is 77% of those initially randomised (n = 1311) or 79% of those who received ≥ 1 dose of study medication (n = 1284). Similarly, 1022 patients completed 24 weeks of follow-up, which is 78% or 80%, respectively (see Methodology section for further explanation). **Compliance:** 27 patients were randomised but not treated	

Outcome: % with response (n)[d]	**24-LD**	**24-SD**	**48-LD**	**48-SD**
Viral response				
End of treatment				
Genotype 1	68% (69/101)	78% (92/118)	60% (150/250)	69% (187/271)
Genotype 2 or 3	94% (90/96)	90% (130/144)	82% (81/99)	85% (130/153)
SVR by genotype and baseline viral load:				
Genotype 1:	29% (29/101)	42% (50/118)	41% (103/250)	52% (141/271)
Low viral load[e]	41% (21/51)	52% (37/71)	55% (33/60)	65% (55/85)
High viral load[f]	16% (8/50)	26% (12/47)	36% (68/190)	47% (88/186)
Genotype 2 or 3:	84% (81/96)	81% (117/144)	79% (78/99)	80% (122/153)
Low viral load[e]	85% (29/34)	83% (39/47)	88% (29/33)	77% (37/48)
High viral load[f]	84% (52/62)	80% (78/97)	74% (49/66)	82% (86/105)

continued

Outcome: % with response (*n*)[d]	**24-LD**	**24-SD**	**48-LD**	**48-SD**
SVR by genotype and baseline fibrosis[g]:				
F3 or F4 fibrosis + genotype 1	26% (6/23)	26% (7/27)	28% (19/67)	41% (32/78)
F3 or F4 fibrosis + genotype 2 or 3	75% (15/20)	74% (29/39)	70% (14/20)	73% (24/33)
F0 or F1 fibrosis + genotype 1	29% (23/78)	46% (42/91)	45% (83/183)	57% (110/193)
F0 or F1 fibrosis + genotype 2 or 3	87% (66/76)	84% (88/105)	81% (64/79)	83% (100/120)

Treatment effects by genotype and baseline viral load	**OR (95% CI)**	***p*-Value**	**Difference in SVR rate (%) (95% CI)**
48 vs 24 weeks of treatment (48-LD and 48-SD vs 24-LD and 24-SD):			
Genotype 1 (n = 740)	2.19 (1.52 to 3.16)[h]	<0.0001	11.2 (3.6 to 18.9)
High viral load[f] (n = 473)	2.90 (1.66 to 5.07)[h]	0.0001	20.9 (11.4 to 30.3)
Low viral load[e] (n = 267)	1.71 (1.05 to 2.80)[i]	0.034	13.2 (1.2 to 25.1)
Genotype 2 or 3 (n = 492)	0.89 (0.56 to 1.42)[i]	>0.2	–2.7 (–9.6 to 4.2)
Standard vs low RBV dose (24-SD and 48-SD vs 24-LD and 48-LD):			
Genotype 1 (n = 740):	1.55 (1.14 to 2.10)[j]	0.005	11.9 (4.7 to 18.9)
High viral load[f] (n = 473)	1.56 (1.06 to 2.29)[k]	0.025	10.4 (1.7 to 19.1)
Low viral load[e] (n = 267)	1.53 (0.93 to 2.52)[k]	0.101	10.4 (–1.8 to 22.4)
Genotype 2 or 3 (n = 492)	1.00 (0.63 to 1.61)[j]	>0.2	–0.7 (–7.8 to 6.3)

Incidence of adverse events, *n* (%)	**24-LD (n = 207)**	**24-SD (n = 280)**	**48-LD (n = 361)**	**48-SD (n = 436)**
Severe adverse events	46 (22)	63 (23)	116 (32)	141 (32)
Serious adverse events	7 (3)	19 (7)	33 (9)	44 (10)
Treatment-related serious adverse events[l]	3 (1)	8 (3)	15 (4)	14 (3)
Deaths	0	1 (<1)	1 (<1)	2 (<1)
Premature withdrawal				
For adverse events/laboratory abnormalities	10 (5)	13 (5)	59 (16)	67 (15)
For insufficient responses[m]	0 (<1)	0 (<1)	31 (9)	24 (6)
For any reason	14 (7)	22 (8)	117 (32)	117 (27)
Reduction or omission of ≥ 1 doses for adverse events/laboratory abnormalities:				
PEG 2a	63 (30)	73 (26)	120 (33)	159 (36)
RBV	39 (19)	76 (27)	101 (28)	166 (38)
Specific adverse events[n]:				
Headache	102 (49)	136 (49)	187 (52)	239 (55)
Fatigue	98 (47)	135 (48)	182 (50)	211 (48)
Myalgia	91 (44)	120 (43)	154 (43)	163 (37)
Pyrexia	81 (39)	114 (41)	156 (43)	173 (40)
Insomnia	69 (33)	99 (35)	146 (40)	146 (33)
Nausea	64 (31)	91 (33)	107 (30)	151 (35)
Rigors	64 (31)	87 (31)	87 (24)	119 (27)
Irritability	59 (29)	76 (27)	96 (27)	112 (26)
Alopecia	53 (26)	74 (26)	106 (29)	92 (21)
Arthralgia	50 (24)	70 (25)	106 (29)	105 (24)
Pruritus	56 (27)	60 (21)	81 (22)	111 (25)
Depression	43 (21)	42 (15)	79 (22)	104 (24)
Diarrhoea	44 (21)	46 (16)	65 (18)	96 (22)
Dermatitis	34 (16)	49 (18)	69 (19)	86 (20)
Decreased appetite	30 (14)	41 (15)	66 (18)	91 (21)

[a] See *Definitions* below for 24-LD, 24-SD, 48-LD and 48-SD.
[b] ALT level divided by the upper limit of normal for the local laboratory value.
[c] Report numbers do not add up to 100% because of rounding, but total only adds up to 87%.
[d] Percentages given in bar chart, numbers calculated by reviewer.
[e] Low viral load, $\leq 2 \times 10^6$ copies/m.
[f] High viral load, $> 2 \times 10^6$ copies/ml.

continued

[g] F3, bridging fibrosis; F4, cirrhosis; F0 or F1, mild fibrosis.
[h] Adjusted for the effect of RBV dose, viral load and study region.
[i] Adjusted for the effect of RBV dose and study region.
[j] Adjusted for the effect of treatment duration, viral load and study region.
[k] Adjusted for the effect of treatment duration and study region.
[l] As judged by investigator.
[m] Patients in 48-LD and 48-SD groups who did not achieve either undetectable HCV RNA or normalisation of ALT levels at week 24 were considered non-responders and discontinued further treatment.
[n] Adverse events related to treatment, as judged by investigators, that occurred in ≥20% of patients who received ≥1 dose of study medication and had ≥1 post-baseline safety assessment.

Additional results:

Virological response:

- Patients treated for 48 weeks were more likely to achieve an SVR than those treated for 24 weeks [48-LD or 48-SD vs 24-LD or 24-SD; OR 1.53 (95% CI 1.17 to 2.01), $p = 0.002$]. Similarly, patients receiving a standard weight-based dose of RBV were more likely to achieve an SVR than those receiving a low dose of RBV [24-SD or 48-SD vs 24-LD or 48-LD; OR 1.41 (95% CI 1.10 to 1.81), $p = 0.01$].
- PEG 2a and standard RBV for 48 weeks produced an overall SVR rate of 63% (95% CI 59 to 68%).
- In multiple logistic regression analysis, HCV genotype was the predominant predictor of response [OR for genotype non-1 vs genotype 1 5.4 (95% CI 4.1 to 7.1), $p < 0.001$]. In addition, the interaction between treatment duration and genotype was highly significant [OR 0.42 (95% CI 0.24 to 0.75), $p = 0.003$].
- The subgroup of patients with/without bridging fibrosis/cirrhosis is too small to draw definitive conclusions.
- 36 patients with genotype 4 were included in the study. At the end of follow-up, SVR rates were obtained in 0% (0/5), 67% (8/12), 63% (5/8) and 82% (9/11) of those randomly assigned to groups 24-LD, 24-SD, 48-LD and 48-SD, respectively.

Safety:

- Most adverse events were mild to moderate in severity and all were typical of those previously reported for IFN and RBV.

Methodological comments:

Allocation to treatment groups: randomisation was centralised, blocked and stratified by geographic region. Patients were randomised unequally to 1 of 4 treatment groups based on genotype and baseline viral load in order to reduce the number of patients with more difficult-to-treat characteristics (genotype 1 and high viral load) who would receive 24 weeks of treatment. After 3 months, it became apparent that the number of patients with genotype non-1 and low viral load could not be recruited within an acceptable time frame, and therefore the randomisation procedure was revised. Patients with genotype 1 and low viral load were initially randomised to groups 24-LD, 24-SD, 48-LD and 48-SD in a 1:2:1:2 ratio, subsequently changed to 1:1:1:1 patients with genotype 1 and high viral load were initially randomised in a 1:1:3:3 ratio, subsequently changed to 1:1:5:5.
Allocation concealment: centralised computer generated randomisation list. Randomisation numbers were allocated sequentially in the order in which patients were enrolled.
Blinding of outcome assessors: study described as double-blind. Investigators and patients were blinded to RBV dose and treatment duration until week 24. A matching placebo tablet identical with the RBV tablets and packaged in identical bottles was provided through a central distribution process to maintain blinding. All patients received the same number of tablets per day (RBV or placebo). Serum HCV RNA and HCV genotyping were determined in a central laboratory.
Analysis by ITT: does not specifically state that it was ITT analysis but all patients who received ≥1 dose of study medication were included in the efficacy analysis ($n = 1284$). Patients without follow-up data were considered not to have achieved an SVR. Patients in groups 48-LD and 48-SD with detectable HCV RNA and elevated ALT levels at week 24 were classified as non-responders and discontinued further treatment.
Comparability of treatment groups at pretreatment: baseline demographics and disease characteristics were generally comparable across treatment groups, with the exception of genotype and viral load (the 48-week groups had a greater proportion of genotype 1 patients and higher viral load). This reflects the unequal stratified randomisation procedure. The differences in baseline HCV RNA levels between strata were reported to be minimal and not clinically meaningful.
Method of data analysis: the results for end of treatment virological response, SVR by genotype and viral load and SVR by genotype and fibrosis stage were presented in bar charts, specifying the virological response rate numerically at the top of each bar with 95% CI shown as vertical bars. The Cochran–Mantel–Haenszel test, stratified by a combination of geographic region, HCV genotype (1 vs non-1), baseline viral load ($\leq 2 \times 10^6$ vs $> 2 \times 10^6$ copies/ml) and RBV dose (800 and 1000–1200 mg/day), was used to compare treatment duration. This test was also used to compare RBV dose, stratified by a combination of region, genotype, viral load and treatment duration. The Breslow–Day test assessed the homogeneity of the ORs over the strata formed by the combination of geographic region, genotype, baseline viral load and RBV dose. Because of the large number of strata (64 strata for the comparisons of treatment duration), the absence of heterogeneity across the strata (lack of treatment group by

continued

strata interaction) could have resulted from insufficient statistical power. For this reason, an alternative test for homogeneity suggested by Breslow and Day was used. Several logistic regression models were conducted to explore further the effect of intervention variables (treatment duration and RBV dose) and several pretreatment factors on the likelihood of achieving an SVR. The following covariates were considered: age, weight, pretreatment ALT quotient, pretreatment HCV RNA levels, gender, race, genotype and fibrosis stage. Nine interaction terms with duration were tested in this model.
Power analysis: assumed that SVRs after 24 weeks of treatment with PEG 2a + RBV, 1000 or 1200 mg/day, would be 70% in patients with genotype non-1 regardless of viral titre, 40% in patients with genotype 1 and low viral titre and 10% in patients with genotype 1 and high viral titre. An improvement of 10–12% in SVR was required to justify extending the treatment duration to 48 weeks in these subgroups. The study had 80% power to detect an improvement in SVR from 70 to 80% patients with genotype non-1, 40 to 52% in patients with genotype 1 and low viral load and 10 to 30% in patients with genotype 1 and high viral load, between the 24- and 48-week treatment groups.
Attrition/drop-out: 1311 patients were initially randomised, 1284 received ≥1 dose of study medication, 1014 completed their allocated treatment, 1022 completed 24 weeks of follow-up. The number discontinuing treatment (n = 270) was reported, with reasons. Patients who withdrew from treatment after 12 weeks or more and had negative HCV RNA levels were encouraged to return for follow-up. For this reason, the number of patients who completed follow-up is higher than the number who completed treatment in 2/4 groups (48-LD and 48-SD).

General comments:
Generalisability: patients appear representative of those with mild chronic HCV without other co-morbidities.
Conflict of interests: the study was supported by Roche, Basel, Switzerland. A large number of the authors had potential conflicts of interest in terms of employment, consultancies, honoraria, grants received or grants pending with Roche and/or Schering-Plough.
Definitions: 24-LD, 24 weeks of therapy with a low dose of RBV; 24-SD, 24 weeks of therapy with a standard weight-based dose of RBV; 48-LD, 48 weeks of therapy with a low dose of RBV; 48-SD, 48 weeks of therapy with a standard weight-based dose of RBV; severe psychiatric disease, treatment with an antidepressant medication or major tranquilliser for major depression or psychosis, respectively, for ≥3 months at any time or a history of a suicide attempt, hospitalisation or period of disability due to psychiatric disease; SVR, undetectable serum HCV RNA level at the end of treatment and during the 12–24 week follow-up.

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Partial
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analysis include an ITT analysis?	Adequate
9. Were losses to follow-up completely described?	Adequate

Appendix 11

Mangia and colleagues:[63] data extraction and critical appraisal

Reference and design	Intervention	Participants	Outcome measures
Mangia *et al.*, 2001[63] **Trial design:** Multicentre RCT **Country:** Italy **Sponsor:** Not reported but RBV provided by Schering-Plough	**Intervention 1:** *n* = 96 IFN 2b (s.c.): Dose: 5 MU 3 times per week Duration: 12 months **Intervention 2:** *n* = 96 IFN 2b (s.c.): Dose: 5 MU 3 times per week Duration: 12 months RBV (oral): Dose: twice daily at a total dose of 1000 mg for patients <75 kg, 1200 mg for patients >75 kg Duration: 12 months	**Total numbers involved:** 192 randomised and analysed **Eligibility:** treatment-naïve patients, raised ALT for at least 6 months, HCV RNA positive, histopathological evidence of chronic hepatitis (liver biopsy taken with previous 6 months of enrolment into study) **Recruitment:** 9 community hospitals in Italy, between April 1997 and June 1998 **Exclusion criteria:** patients with decompensated cirrhosis (i.e. ascites, bleeding varices, encephalopathy, serum albumin <35 g/l, platelet count <100,000/mm^3 and white cell count <3500/mm^3), anaemia (haemoglobin conc <12 g/dl in women and <13 g/dl in men), psychiatric conditions, diabetes, autoimmune diseases, concurrent hepatitis B or HIV infection, high alcohol intake, current i.v. drug use, previous treatment with IFN, pregnancy or concomitant significant medical illness **Baseline measurements:** **Viral load,** mean serum HCV RNA (± SD): no. equivalent genomes/ml (×10^6): 6.2 (± 8.3) Group 1; 6.8 (± 12.2) Group 2 >200,000 equivalent genomes/ml, no. (%): 58 (60%) Group 1; 60 (63%) Group 2 **Serum ALT:** not reported **Histology:** Classification system used: Scheuer Fibrosis stage, no. (%): 0, 1: 148 (77%) > 1: 44 (23%) Necro-inflammation, no. (%): 1, 2: 176 (92%) 3: 16 (8%) Timing of liver biopsy: within the previous 6 months of enrolment into study **Genotypes, no. (%):** 1b: 91 (47%) 2a: 66 (34%) 3: 26 (14%) Others: 9 (5%)	**Primary outcomes:** SVR **Secondary outcomes:** • normalisation of ALT values • adverse events **Length of follow-up:** 6 months post-treatment

continued

Reference and design	Intervention	Participants	Outcome measures
		Gender, no. (%): 128 male (67%), 64 female (33%) **Age (years), mean (± SD):** 49 (± 21) Group 1; 46 (± 24) Group 2 **Ethnic groups, no. (%):** not reported **Mode of infection, no. (%):** Injecting drug use: 40 (21%); Transfusion: 11 (6%); Community acquired: 141 (73%) **Losses to follow-up:** 0 **Compliance:** 174/192 (91%) completed therapy. 18 patients (9%) (10 treated with combination therapy and 8 with IFN alone) stopped treatment for non-compliance (n = 6) or severe side-effects (n = 12)	

Outcome No. with response (%, 95% CI)	IFN 2b (5 MU)	IFN 2b (5 MU) + RBV (1000–1200 mg)	*p*-Value
Viral response:			
12 weeks	42/96 (43.4%)	64/96 (66.7%)	0.001
End of treatment	33/96 (34.4%; 25 to 44)	57/96 (59.4%; 50 to 70)	0.0007
SVR at follow-up	20/96 (20.8%;13 to 29)	52/96 (54.2%; 44 to 64)	0.0001
Biochemical response (ALT normalisation)			
End of treatment	38/96 (39.6%; 30 to 49)	66/96 (68.8%; 60 to 70)	0.0001
End of follow-up	22/96 (22.9%; 15 to 31)	55/96 (57.3%; 48 to 67)	0.0001

Outcome variable no. (%, 95% CI)	IFN 2b (5 MU)	*p*-Value[a]	IFN 2b (5 MU) + RBV (1000–1200mg)	*p*-Value[a]
SVR by genotype:				
1, 4 or 5	7/55 (13%; 4 to 21)	0.005	17/45 (38%; 23 to 51)	0.002
2 or 3	15/41 (36%; 21 to 51)		35/51 (69%; 56 to 81)	
SVR by HCV RNA level				
Low[b]	10/38 (26%; 13 to 40)	0.52	18/37 (49%; 32 to 64)	0.39
High[b]	12/58 (21%; 10 to 31)		34/59 (58%; 45 to 70)	
SVR by age:				
≤40 years	5/33 (15%; 20 to 27)	0.19	20/33 (61%; 44 to 77)	0.35
>40 years	17/63 (27%; 16 to 37)		32/63 (51%; 38 to 63)	
SVR by gender:				
Female	8/37 (22%; 8 to 35)	0.54	14/27 (52%; 33 to 71)	0.77
Male	14/59 (24%; 13 to 34)		38/69 (55%; 43 to 66)	
SVR by fibrosis staging:				
0 or 1	15/77 (19%; 10 to 28)	0.10	45/71 (63%; 52 to 74)	0.004
>1	7/19 (37%; 15 to 58)		7/25 (28%; 10 to 45)	
SVR by necro-inflammation grading:				
1 or 2	48/90 (53%; 43 to 63)	0.52	17/86 (20%; 11 to 28)	0.14
3	4/6 (67%; 28 to 104)		4/10 (40%; 19 to 80)	
SVR by combination of virological factors:				
Genotype				
2, 3 + low viraemia[b]	4/15 (27%; 4 to 49)	0.36	12/17 (71%; 48 to 92)	0.82
2, 3 + high viraemia[b]	11/27 (41%; 22 to 59)		25/34 (74%; 59 to 88)	

continued

Outcome variable no. (%, 95% CI)	IFN 2b (5 MU)	*p*-Value[a]	IFN 2b (5 MU) + RBV (1000–1200mg)	*p*-Value[a]
Genotype				
1, 4, 5 + low viraemia[b]	4/24 (17%; 17 to 31)	0.22	7/22 (32%; 12 to 51)	0.83
1, 4, 5 + high viraemia[b]	2/30 (7%; 0 to 9)		8/23 (35%; 15 to 54)	

Outcome	IFN 2b (5 MU)	IFN 2b (5 MU) + RBV (1000-1200 mg)	*p*-Value
Histology (proportion with improvement)	Not measured	Not measured	
Adverse events:			
Mild neuropsychiatric effects	13/96 (13.5%)	4/96 (4.2%)	
IFN dose discontinuation for			
Any adverse event	8	10	
Anaemia	0	0	

[a] Favourable vs unfavourable baseline features in each treatment group.
[b] Low viraemia, ≤200,000 equivalent genomes/ml; high viraemia: ≥200,000 equivalent genomes/ml.

Additional results:

Virological and biochemical response:

- The virological relapse rate after monotherapy and combination therapy occurred in 13/33 (39.4%; 95% CI 23 to 56) and 5/57 (9%; 95% CI 1 to 16) of end-of-therapy responders respectively ($p = 0.0007$).
- The combined rate of sustained biochemical and virologic response was 22.7% (95% CI 14 to 31) and 60.5% (95% CI 50 to 71) with IFN monotherapy and combination therapy, respectively ($p < 0.0001$).
- At the end of follow-up, normalisation of ALT values was associated with undetectable levels of serum HCV RNA in 98.6% of patients who had an SVR: apart from a single patient in the combination therapy group, 71 patients who had an SVR had persistently normal serum ALT concentrations. Serum HCV RNA levels remained detectable after treatment, despite persistently normal ALT concentration, in 5/77 (6.5%) patients, two cases in monotherapy and three in combination therapy.

Combination of baseline characteristics with response:

- Patients treated with combination therapy were more likely to have an SVR regardless of their baseline characteristics. Patients with baseline features known to negatively influence the response to IFN monotherapy, such as genotype 1, high viraemia levels, male gender, liver fibrosis and age >40 years, when treated with combination therapy had a significantly higher chance of responding than those receiving IFN monotherapy ($p < 0.005$ for each single feature).
- Using univariate analysis, genotype appeared to influence the rate of sustained response in each of the two treatment groups ($p = 0.005$), whereas baseline viraemia, age, gender, presumed source or duration of infection and grading did not ($p > 0.05$). The histological staging affected the response in the combination therapy group ($p = 0.004$).
- Logistic regression analysis indicated that treatment with IFN + RBV was the strongest predictor of response ($\chi^2 = 21.3$: $p = 0.0001$). In addition to treatment regimen, only genotype had an independent effect on a sustained response ($\chi^2 = 19.8$; $p = 0.0001$).

Predictive values of response:

- Examination of the month 3 HCV RNA status in patients with a sustained response showed that the PPV, (the probability that HCV RNA would still be positive at month 6 of follow-up if the HCV RNA was positive at treatment month 3) was 82% (95% CI 67 to 98) for combination therapy patients and 98% (95% CI 94 to 100) for monotherapy patients.
- Viral persistence at month 3 of therapy was a better predictor of non-response to monotherapy (1/50 experienced a late viral clearance) than to combination therapy (4/23 experienced a late viral clearance).
- In IFN monotherapy, normal ALT levels during therapy were unhelpful in predicting a response (NPV <40%), whereas increased ALT concentrations were highly predictive of non-response (PPV = 97% at treatment month 3). In combination therapy patients, ALT levels at treatment month 3 were of better prediction than corresponding values at treatment month 1: normal ALT levels at treatment month 3 predicted a response in 50/69 patients (NPV = 72%), whereas abnormal ALT levels were predictive of a non-response in 15/17 patients (PPV = 88%). Evaluating these levels at treatment month 6 increased these rates in combination therapy patients.

Safety:

- An RBV dose reduction to 600–800 mg was necessary in 12/96 (12.5%) of combination therapy patients when haemoglobin concentrations decreased to 10 g/dl. This did not affect long-term response.
- Flu-like symptoms occurred early in the majority of patients at an equal rate in the two treatments.

continued

- 44/192 (23%) patients had to switch from recombinant IFN 2b to natural leucocyte IFN due to hard to tolerate side-effects: 26 could continue the trial with the new IFN, whereas 18 (10 combination, 8 monotherapy) discontinued therapy by month 6 due to no compliance ($n = 6$), major psychiatric symptoms ($n = 5$), infections ($n = 4$), malaise ($n = 3$). Response rates were not influenced by the change in IFN.

Methodological comments:
- *Allocation to treatment groups:* no details reported on randomisation method. Patients were randomised 1:1.
- *Allocation concealment:* not reported.
- *Blinding of outcome assessors:* testing for HCV RNA was carried out in a single laboratory for all patients. No further details. A single liver pathologist who was unaware of the patient's treatment and response to therapy scored the pretherapy liver biopsies for hepatic inflammation and fibrosis.
- *Analysis by ITT:* reports that data were assessed using ITT analysis. Results were reported for all 192 randomised patients.
- *Comparability of treatment groups at pretreatment:* groups appear comparable at baseline for demographics, duration and source of HCV infection and liver histology. There were some differences in the distribution of genotypes: there were less (42 vs 53%) genotype 1b patients and twice the number of genotype 3 patients (18 vs 9%), in the combination therapy group compared with monotherapy, although the authors report that the distribution of HCV genotypes was similar in the two groups. No *p*-values were presented.
- *Method of data analysis:* baseline demographics and clinical features of the disease were compared with the χ^2 test for discrete variables and Wilcoxon's rank-sum test for continuous variables. Pretherapy features were evaluated by logistic regression analysis without variable selection in order to determine their relatedness with sustained response. All statistical tests were two-tailed.
- *Power analysis:* a sample size of 164 patients was estimated on an α type of error of 0.05 and a β error of 0.10 for a primary two-sided test, on the assumption of 40% response in the combination group and 22% response in the monotherapy group. Expecting a drop-out rate of 10%, 192 patients were included and treated.
- *Attrition/drop-out:* of 192 patients, 174 completed therapy: 18 patients stopped treatment for non-compliance or severe side-effects. No patient was lost to follow-up.

General comments
Generalisability: patients would appear to be representative of patients with mild chronic HCV without other co-morbidities.
Conflict of interests: the Schering-Plough Co. of Italy provided a generous supply of RBV.
Definitions: SVR, defined as the disappearance of HCV RNA at 6 months post-therapy cessation; PPV, patients with positive serum HCV RNA or elevated ALT who do not achieve a response (prediction of non-response); NPV, patients with negative serum HCV RNA or normal ALT who achieve response (prediction of response).

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the patient blinded?	Not applicable as open-label trial
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analysis include an ITT analysis?	Adequate
9. Were losses to follow-up completely described?	Adequate

Appendix 12

Reichard and colleagues:[70] data extraction and critical appraisal

Reference and design	Intervention	Participants	Outcome measures
Reichard *et al.*, 1998[70] **Trial design:** Multicentre, double-blind RCT **Country:** Sweden **Sponsor:** Schering-Plough	**Intervention 1:** *n* = 50 IFN 2b (s.c.): Dose: 3 MU 3 times per week Duration: 24 weeks RBV (oral): Dose: twice daily at a total dose of 1000 mg for patients ≤75 kg, 1200 mg for patients >75kg Duration: 24 weeks **Intervention 2:** *n* = 50 IFN 2b (s.c.): Dose: 3 MU 3 times per week Duration: 24 weeks Placebo: Dose: twice daily Duration: 24 weeks	**Total numbers involved:** 100 randomised and analysed **Eligibility:** persistently raised aminotransferases for at least 6 months, serum antibodies to HCV, detectable HCV RNA, biopsy findings (taken in preceding 12 months) consistent with a diagnosis of chronic hepatitis **Recruitment:** 5 university hospitals in Sweden between March and June 1995 Exclusion criteria: age <18 or >70 years, previous treatment with IFN 2b or RBV, history of alcohol abuse or haemolytic disease, decompensated cirrhosis, autoimmune hepatitis, chronic hepatitis B infection, HIV infection, current i.v. drug use, drug-related liver disease, pregnancy **Baseline measurements:** **Viral load,** geometric mean HCV RNA × 10^6 (± SD), Eq/ml: 4.06 Group 1, 3.20 Group 2 **ALT**, mean (± SD), IU/l: 156 (± 114) Group 1, 138 (± 90) Group 2 **Histology:** Classification system used: Batts and Ludwig/Sciot and Desmet Fibrosis score, mean (± SD): 1.6 (± 0.7) Group 1, 1.4 (± 0.7) Group 2 Cirrhosis: 13 (13%) Necro-inflammatory score, mean (± SD): 1.4 (± 0.5) Group 1, 1.3 (± 0.5) Group 2 Timing of liver biopsy: obtained in the preceding 12 months and at week 24 **Genotypes, no. (%):** 1a: 17 (17%) 1b: 19 (19%) 1 (not subtyped): 3 (3%) 1a + b: 5 (5%) 2a: 1 (1%) 2b: 17 (17%) 2a + b: 1 (1%) 3a: 33 (33%) 4 (not subtyped): 2 (2%) 4c + d: 1 (1%) 5a: 1 (1%)	**Primary outcomes:** SVR **Secondary outcomes:** • biochemical response • histological response • adverse effects **Length of follow-up:** 24 weeks after completion of therapy

continued

Reference and design	Intervention	Participants	Outcome measures
		Gender, no. (%): male 62 (62%), female 38 (38%) **Age (years), mean (± SD):** 39.6 (± 9.6) Group 1, 39.4 (± 7.5) Group 2 **Ethnic groups, no. (%):** not reported **Mode of infection, no. (%):** Injection drug use: 51 (51%) Transfusion: 16 (16%) Unknown: 33 (33%) **Losses to follow-up:** 90/100 patients (90%) completed 24 weeks of treatment. 3 patients (3%) were lost to follow-up. Liver biopsies were available from 99 patients before treatment, and from 90 at the end of treatment **Compliance:** 1 patient (1%) discontinued treatment due to i.v. drug use; 7 refused a second biopsy	

Outcome % with response (*n*)	IFN 2b (3MU) + RBV (1000–1200 mg)	IFN 2b (3MU) + placebo	*p*-Value (between-group comparison)
Viral response:			
End of treatment	52% (26/50)	52% (26/50)	1.00
SVR at follow-up	36% (18/50)	18% (9/50)	0.047
SVR by genotype:			
1a	36% (4/11)	17% (1/6)	0.60
1b	13% (1/8)	9% (1/11)	1.00
1 not sub-typed/1a + b	0/3	0/5	
2	43% (3/7)	25% (3/12)	0.62
3a	53% (10/19)	21% (3/14)	0.09
SVR by baseline viral load (Eq/ml)[a]:			
$<1 \times 10^6$	45% (5/11)	45% (5/11)	1.00
$1–2.99 \times 10^6$	10% (1/10)	23% (3/13)	0.60
$3–7.99 \times 10^6$	10% (1/10)	0/13	1.00
$8–19.99 \times 10^6$	62% (8/13)	13% (1/8)	0.07
$\geq 20 \times 10^6$	50% (3/6)	0/5	0.18
Biochemical response:			
End of treatment	66% (33/50)	56% (28/50)	0.41
End of follow-up	44% (22/50)	24% (12/50)	0.057
Histology, mean (± SD):			
Inflammation (grade score):			
Before treatment	1.4 (± 0.5)	1.3 (± 0.5)	
End of treatment	0.9 (± 0.5)	0.8 (± 0.7)	<0.001
Fibrosis (stage score)	No change	No change	
Adverse events, % (no. of patients):			
Dose discontinuation for			
Any adverse event	8% (4/50)	6% (3/50)	
Other[b]	6% (3/50)		
Dose reduction for			
Any adverse event	14% (7/50)	0	
Anaemia	2% (1/50)	0	
Neutropenia	2% (1/50)	6% (3/50)	
Dose reduction or discontinuation	32% (16/50)	12% (6/50)	0.03

continued

Outcome % with response (*n*)	IFN 2b (3MU) + RBV (1000–1200 mg)	IFN 2b (3MU) + placebo	*p*-Value (between-group comparison)
Specific adverse events, % (no. of patients):			
Fatigue	90% (45/50)	78% (39/50)	0.11
Nausea	34% (17/50)	12% (6/50)	0.02

[a] DNA assay.
[b] Lost to follow-up.

Additional results:

Virological and biochemical response

- Neither eradication of viraemia nor geometric mean HCV RNA concentrations differed significantly between the groups during the treatment period, but did differ significantly by week 48 ($p < 0.05$).
- 4 patients with biochemical sustained responses were classified as virological non-responders although HCV RNA was negative at follow-up. 2 patients in the IFN + RBV group were HCV RNA negative at week 12, positive in very low concentrations at week 24 and negative at week 48; 2 patients (1 in each group), who had declining positive HCV RNA concentrations at weeks 12 and 24 became HCV RNA negative at week 48. One year after treatment stopped, all 4 patients had no detectable HCV RNA and normal serum amino transaminase concentrations, which suggests that they had an SVR. If these patients are included, the SVR rate in the IFN + RBV group is 42% (21/50) vs 20% (10/50) in the IFN + placebo group ($p = 0.03$).
- In the IFN + RBV group, baseline HCV RNA concentrations were significantly lower in the SVR group than in those who did not achieve an SVR (geometric mean 0.95×10^6 vs 4.17×10^6 Eq/ml, $p = 0.008$); whereas HCV genotype, liver histology score, sex and age did not affect the SVR rate.
- In the IFN + placebo group, no baseline factor predicted an SVR.
- The SVR was significantly greater in patients with a baseline viral load $>3 \times 10^6$ Eq/ml who received IFN + RBV compared with those who received IFN + placebo, 41% (12/29) vs 4% (1/26), $p = 0.009$.

Histological response

- No difference in histological improvement between the groups was found.
- The greatest reduction in mean grade score was seen in the patients with a sustained response but was also significant in patients with non-sustained or no response to treatment.

Safety

- Other side-effects were experienced by patients, but did not differ between treatment groups and the data are not shown. They include headache, myalgia, arthralgia, fever, vertigo, abdominal pain, anorexia, depression, irritability, insomnia, alopecia, pruritus, coughing, hypothyroidism and hyperthyroidism.

Methodological comments:

Allocation to treatment groups: randomly generated numbers were placed in individually sealed envelopes that were distributed by a central pharmacy to the individual centres in blocks of 10 (5 RBV and 5 placebo). Does not report how the numbers were randomly generated.
Allocation concealment: central randomisation procedure. The randomisation code was not broken until all patients had completed the follow-up period.
Blinding of outcome assessors: study described as double-blind. Patients received RBV or a matched placebo. Liver biopsies were scored by a single blinded pathologist. No details are reported re the outcome assessors for the virological assays.
Analysis by ITT: reports that data were analysed by ITT. Results were reported for all 100 randomised patients. Patients who discontinued treatment or were lost to follow-up were classified as non-responders.
Comparability of treatment groups at pretreatment: groups were not significantly different at baseline for demographic, biochemical and histological characteristics (*p*-values presented).
Method of data analysis: baseline characteristics were compared by Student's *t*-test. Quantitative variables were tested by the Mann–Whitney *U*-test, the paired *t*-test and the two-sample Wilcoxon signed-rank test where appropriate. Fisher's exact two-tailed test was used to compare categorical variables.
Power analysis: with a power of 80% at the 5% significance level, a sample size of 100 patients was needed to show a difference between treatment groups and to allow for a 20% drop-out rate.
Attrition/drop-out: 90 patients (90%) completed 24 weeks of treatment. 7 patients (7%) discontinued treatment (reasons given) and 3 patients (3%) were lost to follow-up. Biopsy samples were available for 99 patients pretreatment and 90 patients at the end of treatment. 7 patients refused a second biopsy; 1 pretreatment and 3 post-treatment biopsy samples were too small to allow a valid evaluation.

continued

General comments
Generalisability: patients seem representative of those with mild chronic HCV without other co-morbidities.
Conflict of interests: the study was supported by grants from Schering Plough AB, Sweden and Schering Plough International.
Definitions: SVR, the absence of HCV RNA on PCR at both weeks 24 and 48; biochemical response, serum aminotransferase concentrations within the normal range.

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Partial
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
8. Did the analysis include an ITT analysis?	Adequate
9. Were losses to follow-up completely described?	Adequate

Appendix 13

Verbaan and colleagues:[64] data extraction and critical appraisal

Reference and design	Intervention	Participants	Outcome measures
Verbaan *et al*., 2002[64] **Trial design:** RCT **Country:** Sweden **Sponsor:** Schering-Plough AB, Sweden	**Intervention 1:** *n* = 57 IFN 2b: Dose: 3 MU three times per week s.c. Duration: 52 weeks Ribavirin (oral): Dose: 1000 mg per day for patients ≤75 kg, 1200 mg per day for patients >75 kg Duration: 52 weeks **Intervention 2:** *n* = 59 IFN 2b: Dose: 3 MU three times per week s.c. Duration: 52 weeks Placebo: Dose: twice daily Duration: 52 weeks	**Total numbers involved:** 128 randomised. 116 started treatment and analysed **Eligibility:** • Previously untreated adults aged 18–60 years, with histologically mild chronic HCV infection • HCV RNA positive in serum or plasma, liver biopsy within the previous 12 months showing a mild histological picture, and raised ALT for at least 6 months • Knodell activity score between ≥1 and ≤6 with periportal piecemeal necrosis ± bridging necrosis ≤3; interlobular degeneration and focal necrosis ≤3 and portal inflammation ≤4 • Only patients with a fibrosis stage of ≤1 could be included **Recruitment:** 15 centres for gastroenterology or infectious diseases in Sweden between February 1997 and July 1998 **Exclusion criteria:** • PNALT • Clinical or serological evidence of: active hepatitis B infection or HIV infection metabolic or autoimmune liver diseases immunologically mediated diseases chronic pulmonary disease heart disease serious mental disease or a seizure disorder inadequate levels of haemoglobin (<115 g/l for females, <130 g/l for males) platelet count $<100 \times 10^9$ /l white blood count $<3 \times 10^9$ /l granulocyte count $<1.5 \times 10^9$ /l pregnancy or breast feeding malignancy • History of intravenous drug abuse within the previous 12 months or ongoing alcohol abuse (>50 g of alcohol per day) **Baseline measurements:** **Viral load:** geometric HCV RNA bDNA version 3, copies/ml: Group 1: 2.34×10^6 Group 2: 9.16×10^5	**Primary outcomes:** • HCV RNA negativity by PCR in both serum and in liver tissue 26 weeks post-treatment **Secondary outcomes:** • Haematological and biochemical parameters • Clinical signs and side-effects • Liver histology **Length of follow-up:** 26 weeks after treatment was discontinued

continued

Reference and design	Intervention	Participants	Outcome measures
		Histology: Knodell score Mean grade (range): Group 1, 4.3 (1–6); Group 2, 3.9 (1–6) Mean stage: Group 1, 0.4; Group 2, 0.3 Timing of liver biopsy: not reported **Genotypes (proportions):** 1a: Group 1 35%, Group 2 35% 1b: Group 1 12%, Group 2 16% 2b: Group 1 17%, Group 2 14% 3a: Group 1 30%, Group 2 33% 4: Group 1 2% 1b + 3a: Group 1 2% Unknown: 2% **Gender (% male):** Group 1 64%, Group 2 58% **Age, mean (range):** Group 1 38 years (20–55), Group 2 36 years (23–49) **Ethnic groups:** not reported **Mode of infection (%):** Intravenous drug use: Group 1 65%, Group 2 56% Transfusion: Group 1 7%, Group 2 10% Other: Group 1 5%, Group 2 9% Unknown: Group 1 23%, Group 2 25% **Losses to follow-up:** Seven patients dropped out before starting treatment; 5 were excluded because of incorrect inclusion. Week 52: sera from 6 patients missing. Week 78: sera from 17 patients missing. HCV RNA in liver tissue analysed in 17 cases. Liver biopsy week 78 performed on 81 patients, 13 lost to follow-up **Compliance:** not reported	

Outcome	Intervention 1	Intervention 2	*p*-Value
Number HCV RNA negative, end of treatment (week 52) ($n = 94$)[a]	28	19	
Number with a viral breakthrough	4 (weeks 27–52)	9	
SVR in plasma at follow-up (week 78) ($n = 99$)[b]	54.4% (31/57)	20.3% (12/59)	<0.001
Relapse during follow-up	3	5	
SVR by genotype at follow-up:			
1	8 (28%)	1 (4%)	0.014
Non-1	22 (81%)	10 (36%)	0.003
Not included	1	1	
Viral load at baseline:			
Sustained responders:			
Genotype 1	1.9×10^5	3.3×10^5	
Genotype non-1	6.4×10^5	5.3×10^5	
All	4.6×10^5	5.9×10^5	

continued

Outcome	Intervention 1	Intervention 2	*p*-Value
Non-responders:			
Genotype 1	2.5×10^6	2.9×10^6	
Genotype non-1	8.2×10^5	4.1×10^6	
All	2.0×10^6	2.4×10^6	
Histology ($n = 81$), mean grade:			
Sustained responders:	($n = 30$)	($n = 9$)	
At entry	4.3	4.1	
At follow-up	1.3	1.3	
p-Value (entry vs follow-up)	<0.00	0.018	
Non-responders:	($n = 15$)	($n = 27$)	
At entry	3.4	4.4	
At follow-up	3.5	4.9	
p-Value (entry vs follow-up)	NS	NS	
Adverse events:			
Dose discontinuation for:			
Serious adverse events	3 (1 related to study treatment – visual defect in right eye due to hypertension)	0	
Depression	1	0	
Headache	0	1	
Myalgia	0	1	
Cough	1	0	
Fatigue	1	1	
Dose reduction for:			
Anaemia	4	0	
Psychiatric side-effects	3	1	
Neutrophil count $< 1.5 \times 10^9$/l	1	0	
Diarrhoea	1	0	
Myalgia	1	0	
Fatigue	1	0	
Hypothyroidism	1	0	
Dizziness	1	0	
Vomiting	1	0	
Alopecia	0	1	
Discontinuation of treatment:			
HCV RNA positive at week 26 (in accordance with protocol)	18	24	
Other reasons for discontinuation of treatment:			
Non-compliance with protocol (i.v. drug or alcohol abuse)	1	2	
By patient without specific reason	1	4	
Myoma operation	0	1	

[a] Authors report that at 52 weeks, 94 patients were tested for HCV RNA (groups not specified).
[b] At follow-up, HCV RNA was tested in 99 patients while sera from 17 patients were missing, all being classified as HCV RNA positive.

Additional results

- Liver tissue analysed in 74 cases. All but one with SVR were HCV RNA negative in both plasma and liver tissue. All patients with detectable HCV RNA in plasma were also HCV RNA positive in liver tissue.
- All except 12 patients reported at least one adverse event, the majority being classified as mild to moderate even where patients discontinued treatment. A flu-like syndrome with fever, fatigue, headache and myalgia was the most common, followed by alopecia, anorexia and depression, which did not differ between treatment groups.
- Histology: the low fibrosis stage did not change in either group, irrespective of treatment results (data not shown).

Methodological comments:

- *Allocation to treatment groups:* Patients were randomly assigned to one of two treatment arms in blocks of two, according to a computed-generated list.
- *Allocation concealment:* Computer-generated list set up by a central pharmacy.
- *Blinding of outcome assessors:* Study described as double blind. Liver histology was assessed by the same pathologist who was unaware of the patients' assignment or treatment response. No further details.
- *Analysis by ITT:* yes, for patients who started treatment ($n = 116$) but not all those randomised ($n = 128$).
- *Comparability of treatment groups at pretreatment:* No difference in sex, age, HCV genotypes, geometric mean HCV RNA level or histological grade and stage.
- *Method of data analysis:* χ^2 or Fisher's exact test was used to determine the two-tailed statistical significance of differences between proportions in 2×2 tables. Student's *t*-test used for normally distributed continuous variables and Mann–Whitney *U*-test used when skewed. A *p*-value less than 0.05 was taken to be indicative of statistical significance.
- *Power analysis:* Sample size was calculated assuming a complete, sustained response to IFN monotherapy of 25%, compared with a 50% response for combination therapy with IFN–RBV. With a power of 80% at the 5% significance level, a sample size of 65 patients in each group would be required to allow for a 25% dropout rate.
- *Attrition/drop-out:* Study protocol stated that treatment was to be stopped if serum HCV RNA was still detectable after 6 months of therapy; however, all patients were to be monitored for the planned follow-up.
- At 6 months post-treatment, 13 patients were lost to follow-up: 6 discontinued treatment before week 26 and the remainder refused a second liver biopsy.

General comments

Generalisability: Patients with mild HCV infection without comorbidities or clinical signs of liver disease.
Conflict of interests: Grants were received from Schering-Plough AB, Sweden.

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
8. Did the analysis include an ITT analysis?	Adequate
9. Were losses to follow-up completely described?	Partial

Appendix 14

Wright and colleagues:[65] data extraction and critical appraisal

Reference and design	Intervention	Participants	Outcome measures
Wright *et al.*, 2005[65] **Trial design:** Multicentre, unblinded, RCT **Country:** UK **Sponsor:** HTA Programme	**Intervention 1:** *n* = 98 IFN 2b (s.c.): Dose: 3 MU 3 times per week Duration: 48 weeks RBV (oral): Dose: 1000 mg daily for patients <75 kg, 1200 mg daily for patients >75 kg Duration: 48 weeks Both drugs were commenced at the same time **Intervention 2:** *n* = 98 No treatment	**Total numbers involved:** 286 screened, 204 randomised, 196 analysed (attended baseline visit) **Eligibility:** treatment-naïve, adult patients with mild chronic hepatitis C (Ishak necro-inflammatory score ≤ 3, fibrosis score ≤ 2), serum positive for HCV, normal or raised ALT **Recruitment:** 13 centres in the UK, between January 1999 and January 2002 **Exclusion criteria:** liver disease of other aetiology, HIV coinfection, ongoing psychiatric morbidity, i.v. drug use, excessive alcohol intake (>28 units for men, >21 units for women), cardiovascular disease, uncontrolled diabetes mellitus, haemophilia, organ transplant, autoimmune disease, unwillingness to practice contraception **Baseline measurements:** **Viral load,** IU/ml[a]: $<4 \times 10^5$: 56/98 (57%) treated patients $>4 \times 10^5$: 42/98 (43%) treated patients Not reported for control patients **ALT:** Normal: 35/91 (38%) treated patients Raised: 56/91 (62%) treated patients Not reported for control patients **Histology:** Classification system used: Ishak Fibrosis score, mean (± SD): 1.01 (± 0.77) treated patients 1.18 (± 0.79) control patients Necro-inflammatory score, mean (± SD): 1.96 (± 1.06) treated patients 2.2 (± 0.99) control patients Timing of liver biopsy: within 1 year prior to screening visit **Genotypes (proportions):** 1: 101 (52%) Non-1: 95 (48%) **Gender:** 119 male (61%), 77 female (39%) **Age, mean (± SD):** 40.68 (± 8.82) treated patients 40.71 (± 8.29) control patients	**Primary outcomes:** SVR (HCV RNA) **Secondary outcomes:** • adverse events • quality of life **Length of follow-up:** 24 weeks post-intervention

continued

Reference and design	Intervention	Participants	Outcome measures
		Ethnic groups: White: 177 (90%) Non-white: 14 (7%) Not recorded: 5 (3%) **Mode of infection:** Injection drug use: 104 (53%) Blood products: 31 (16%) Unknown: 61 (31%) **Losses to follow-up:** end of treatment data available for 97/98 treated patients and 87/98 control patients; 24-week follow-up period completed for 91/98 treated patients and 87/98 control patients (*NB* on ITT analysis) **Compliance:** The length of time on therapy was variable and not all patients were able to complete the full treatment protocol	

Outcome	IFN 2b (3 MU) + RBV (1000–1200 mg)	No treatment	*p*-Value (subgroups of treatment arm)
Viral response:			
4 weeks	–	–	–
12 weeks	–	–	–
End of treatment	44% (43/98)	0	–
SVR at follow-up	33% (32/98)	0/98	≤0.00001
SVR by genotype:			
1	18% (9/51)	0/50	0.02
Non-1	49% (23/47)	0/48	
SVR by gender:			
Male	39% (23/59)	0/56	0.47
Female	28% (9/32)	0/42	
SVR by age:			
>40 years	32% (14/44)	0/47	0.65
<40 years	38% (18/47)	0/51	
SVR by ALT:			
Normal	34% (12/35)	0/42	0.92
Raised	36% (20/56)	0/56	
SVR by viral load[a]:			
$<4 \times 10^5$	34% (19/56)	ND	0.82
$>4 \times 10^5$	31% (13/42)		
Histology (proportion with improvement)	Not measured	Not measured	
Adverse events[b]:			
Flu-like symptoms	41	9	
Depression/low mood	48	14	
Sensitive skin	51	16	
Blood abnormality	31	0	
Insomnia	20	21	
Total events	770	257	
Dose discontinuation for any adverse event	10	0	
Dose reduction for any adverse event	46	0	
Hospitalisations	4	0	

[a] 1 IU is equivalent to approximately five RNA copies.
[b] Five most common adverse events listed.

Additional results:

- Logistic regression analysis of all treated patients showed that only viral genotype was an independent predictor for SVR ($p = 0.002$).
- Quantitative virology was performed on 75 patients (51 treated, 17 control patients) (those who attended 5/6 initial early visits and for whom there was a follow-up sample at 24 weeks post-therapy). Patients had a 57% PPV of achieving an SVR if there was a 2-log viral load drop at 12 weeks ($n = 54$); no patient who failed to achieve a 2-log drop ($n = 21$) went on to SVR.
- Quality of life (SF-36): data were available for 24/32 (75%) of the SVRs, 44/68 (65%) of the non-SVRs and 58/98 (56%) of the control group. Data were unavailable for those patients who had failed to attend their post-week 24 visits, and for those who had not filled in the questionnaires correctly. At 24 weeks after end of treatment, there was a mean improvement in 7/8 of the SF-36 scales in SVRs (significant for bodily pain, general health and vitality, $p = 0.01$ vs controls), in 5/8 scales in non-SVRs and in 0/8 scales in control group, where substantial reductions were seen.
- 67% (16/24) of SVRs, 61% (27/44) of non-SVRs and 41% (24/58) of controls reported an improvement in the PCS ($p < 0.05$ for SVRs and non-SVRs vs controls).
- There was an overall deterioration in the role function emotional scale in the SVRs, which was significantly different to the improvement seen in the non-SVRs ($p < 0.05$).
- There were no statistical differences in the MCS.
- There were significant inverse correlations between baseline PCS and the change in PCS in both the SVRs ($R = –0.46$, $p = 0.02$) and non-SVRs ($R = –0.45$, $p = 0.002$) but not the controls. This suggests that individuals with low well-being scores prior to treatment saw a sustained improvement 24 weeks after therapy, regardless of virological outcome. In contrast, patients with preserved baseline well-being scores experienced no long-term improvement.

Methodological comments:

- *Allocation to treatment groups:* randomisation was stratified within centres according to viral genotype (1 vs non- 1). No details reported on actual randomisation method.
- *Allocation concealment:* central randomisation procedure.
- *Blinding of outcome assessors:* qualitative and quantitative virological assays were performed centrally (blinding not specifically mentioned).
- *Analysis by ITT:* yes, for all patients who received at least one dose of study medication ($n = 98$ in each arm). At the end of the trial, 13 treated patients and 24 control patients failed to attend their final visit – all were recorded as being PCR positive in line with the ITT principle.
- *Comparability of treatment groups at pretreatment:* no statistically significant demographic, histological, haematological or biochemical differences at baseline (*p*-values presented).
- *Method of data analysis:* Treatment responses were compared using the χ^2 test. Relationships between pretreatment variables and outcomes were assessed using stepwise logistic regression. Viral load was plotted as a logscale against time for each individual patient. Sensitivity and specificity for presence or absence of a 2-log viral load drop and prediction of SVR were calculated and tabulated for each time point; the optimal time point was determined by receiver-operating characteristic curves. SF-36 scales: analysis of variance used for continuous parametric data and Kruskall–Wallis test used when data was not normally distributed; pairwise comparisons made using a Student's *t*-test or Mann–Whitney *U*-test as appropriate.
- *Power analysis:* to achieve a power of 80% to detect an SVR, expected to be 38%, with a precision of ±5% required 115 patients per group.
- *Attrition/drop-out:* 11/98 control patients declined to participate further after learning of their randomisation to no treatment. Patients who dropped out prior to the final follow-up visit were classified as having failed to respond; patients with no data were classified as 'no clearance'.

General comments

- *Generalisability:* patients would appear to be representative of those with mild chronic HCV without other co-morbidities.
- *Conflict of interests:* RBV was provided as a gift by Schering Plough.
- *Other:* the paper states that "13 treated patients and 28 control patients failed to attend the final post-week 24 visit". However, these numbers do not tally with the patient flow-chart presented on p. 60.
- *Definitions:* mild chronic hepatitis C, Ishak necroinflammatory score ≤3, fibrosis score ≤2; SVR, defined as the absence of serum HCV RNA at 24 weeks post-treatment cessation; non-SVR patients, treatment failures, including non-responders and relapsed patients; PPV, the chance of achieving an SVR.

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the patient blinded?	Not applicable as trial was open-label
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
8. Did the analysis include an ITT analysis?	Adequate
9. Were losses to follow-up completely described?	Adequate

Appendix 15

Zeuzem and colleagues:[66] data extraction and critical appraisal

Reference and design	Intervention	Participants	Outcome measures
Zeuzem *et al.*, 2004[66] **Trial design:** Open-label, multicentre RCT **Country:** International **Sponsor:** Roche	**Intervention 1:** *n* = 212 PEG IFN 2a, 40 kDa (s.c.): Dose: 180 μg once weekly Duration: 24 weeks RBV (oral): Dose: 400 mg twice daily Duration: 24 weeks **Intervention 2:** *n* = 210 PEG 2a, 40 kDa (s.c.): Dose: 180 μg once weekly Duration: 48 weeks RBV (oral): Dose: 400 mg twice daily Duration: 48 weeks **Intervention 3:** *n* = 69 No treatment Randomised in a 3:3:1 ratio	**Total numbers involved:** 514 randomised, 491 analysed **Eligibility:** treatment-naïve patients, aged ≥18 years, positive antibody to HCV antibody test, detectable serum HCV RNA, biopsy findings consistent with a diagnosis of chronic hepatitis C, PNALT levels **Recruitment:** 70 centres in Australia, Europe, New Zealand, North and South America **Exclusion criteria:** no histological evidence of liver disease, ≥1 elevated ALT values (i.e. >ULN) within previous 18 months, patients with transition to cirrhosis or cirrhosis on biopsy, history of bleeding from oesophageal varices, other conditions consistent with decompensated liver disease, neutropenia (absolute neutrophil count <1500 cells/mm^3), thrombocytopenia (<90,000 platelets/mm^3), anaemia (haemoglobin concentration <12 g/dl in women and <13 g/dl in men), serological evidence of infection with HIV or hepatitis A or B, serum creatinine level >1.5 times the ULN, organ transplant recipients, severe cardiac disease, history of severe psychiatric disease (especially depression), evidence of drug abuse (including excessive alcohol intake) within preceding year, other serious systemic disease **Baseline measurements:** **Viral load,** mean HCV RNA level ×10^3 IU/ml (± SD): 1222 (± 1452) Group 1 1055 (± 1287) Group 2 1303 (± 1302) Group 3 **ALT,** maximum mean value,[a] IU/l (± SD): 23.7 (± 6.7) Group 1 24.5 (± 6.4) Group 2 23.9 (± 4.9) Group 3 **Histology:** Classification system used: Ishak	**Primary outcomes:** SVR (at the end of the 24-week untreated follow-up for Groups 1 and 2) **Secondary outcomes:** adverse events Length of follow-up: 72 weeks, representing 48 weeks of follow-up after 24 weeks of therapy (Group 1), 24 weeks of follow-up after 48 weeks of therapy (Group 2), or 72 weeks of untreated follow-up (Group 3)

continued

Reference and design	Intervention	Participants	Outcome measures
		Fibrosis score, no. (%): 0–1: 338 (69%) 2: 98 (20%) 3-4: 49 (10%) >4: 1 (<1%) Missing values: 5 (<1%) Mean fibrosis score (± SD): 1.2 (± 1.02) Group 1 1.2 (± 1.0) Group 2 1.0 (± 0.85) Group 3 Total mean fibrosis score = 1.4 Necro-inflammation score, mean (± SD): 3.7 (± 1.87) Group 1 3.5 (± 1.80) Group 2 3.3 (± 1.56) Group 3 Timing of liver biopsy: obtained within 36 months before study onset **Genotypes, no (%):** Type 1: 332 (68%) 1a: 191 (39%) 1b: 139 (28%) Other: 2 (<1%) Type non-1: 159 (32%) 2: 92 (19%) 3: 44 (9%) 4: 19 (4%) 5: 1 (<1%) 6: 3 (<1%) **Gender:** 198 male (40%), 293 female (60%) **Age (years), mean (± SD):** 43.8 (± 10.0) Group 1 43.9 (± 9.7) Group 2 41.0 (± 10.2) Group 3 **Ethnic groups, no. (%):** White: 420 (86%) Black: 40 (8%) Asian: 12 (2%) Other: 19 (4%) **Mode of infection, no. (%):** Injecting drug use: 151 (31%) Transfusion: 114 (23%) Other: 67 (14%) Unknown: 159 (32%) **Losses to follow-up:** In total, 370/514 (72%) patients initially randomised completed the study **Compliance:** 19 patients were randomised but not treated; 78 patients withdrew prematurely	

continued

Outcome	Group 1 (24 weeks)	Group 2 (48 weeks)	Risk difference (95% CI)	RR, 48 weeks vs 24weeks (95% CI)
Viral response (%):				
End of treatment	–	–	–	–
SVR at follow-up	63/212 (30%; 23.6 to 35.9)[b]	109/210 (52%; 45.1 to 58.7)[b]	22 (13 to 31)	1.7 (1.4 to 2.2), $p < 0.001$
SVR as a function of genotype and baseline viral load[c]:				
Genotype 1 (%):	19/144 (13%; 7.7 to 18.7)[b]	57/141 (40%; 32.3 to 48.5)[b]	27 (17 to 37)	3.1 (1.9 to 4.9), $p < 0.001$
Low viral load	14/87 (16)	42/89 (47)		
High viral load	5/55 (9)	14/51 (27)		
Non-1 genotypes (%):	44/68 (65)	52/69 (75)		
Low viral load	25/36 (69)	30/38 (79)		
High viral load	19/32 (59)	22/31 (71)		
Genotypes 2 or 3 (%):	42/58 (72%; 60.9 to 83.9)[b]	46/59 (78%; 67.4 to 88.5)[b]	6 (–10 to 21)	1.1 (0.9 to 1.3), $p = 0.452$
Low viral load	24/30 (80)	25/31 (81)		
High viral load	18/28 (64)	21/28 (75)		
Genotype 4 (%):	1/8 (13)	5/9 (56)		
Low viral load	1/6 (17)	4/6 (67)		
High viral load	0/2 (0)	1/3 (33)		

Outcome	Group 1 (24 weeks, $n = 212$)	Group 2 (48 weeks, $n = 210$)	Group 3 (control, $n = 69$)
Histology (proportion with improvement)	Not measured	Not measured	Not measured
Adverse events (%):			
Any adverse event:	209 (99)	207 (99)	53 (77)
Severe adverse events	56 (26)	70 (33)	10 (14)
Life-threatening adverse events	3 (1)	8 (4)	2 (3)
Treatment-related adverse events	204 (96)	206 (98)	NA
Serious adverse events:	18 (8)	34 (16)	4 (6)
Treatment-related serious adverse events	6 (3)	20 (10)	NA
Deaths	0	0	1
Premature withdrawal for adverse events or laboratory abnormalities	15 (7)	38 (18)	NA
Dose modification for adverse events:			
PEG 2a	23 (11)	40 (19)	NA
RBV	42 (20)	62 (30)	NA
Dose modification for laboratory abnormalities:			
PEG 2a	33 (16)	47 (22)	NA
RBV	19 (9)	45 (21)	NA
Specific adverse events[d]:			
Headache	93 (44)	117 (56)	5 (7)
Fatigue	109 (51)	107 (51)	12 (17)
Myalgia	81 (38)	93 (44)	5 (7)
Pyrexia	64 (30)	90 (43)	2 (3)
Insomnia	74 (35)	76 (36)	5 (7)
Nausea	68 (32)	84 (40)	1 (1)
Arthralgia	68 (32)	62 (30)	3 (4)

[a] Maximum of the 3 measurements that qualified a patient for the trial.
[b] Ranges are 95% CI.
[c] Low, ≤800,000 IU/ml; high, >800,000 IU/ml. Viral response, baseline measurements were missing for 3 patients with genotype 1.
[d] Adverse events for which the incidence was >20% in at least one study group (7 most common listed).

Additional results:
- No patient in the untreated control group (Group 3) cleared HCV.
- Prognostic factors for SVR:
- In genotype 1 patients, treatment duration (24 vs 48 weeks: OR 4.39, 95% CI 2.42 to 7.98) and baseline viral load ($>8 \times 10^5$ vs $\leq 8 \times 10^5$ IU/ml: OR 2.21, 95% CI 1.20 to 4.09) significantly and independently affected SVR rates.
  In genotype 1 patients with a baseline HCV RNA concentration $\leq 8 \times 10^5$ IU/ml, the unadjusted probability of achieving an SVR was 77% higher than in patients with a viral load $>8 \times 10^5$ IU/ml (unadjusted RR 1.77, 95% CI 1.12 to 2.82).
  For non-1 genotype patients, age was the only independent variable that was significantly associated with SVR rates (≤40 years vs >40 years: OR 2.31, 95% CI 1.02 to 5.24). Patients aged ≤40 years had a 26% higher probability of achieving an SVR compared with patients aged >40 years (RR 1.26, 95% CI 1.02 to 1.55).
- Adverse events were generally mild in severity, and no new adverse events were identified.
- Transient elevations in ALT activity were detected in treated and control patients during the study. The majority of moderate elevations coincided with virological relapses in treated patients. Median ALT activity remained stable in untreated control patients but decreased up to 10 IU/l in treated patients and remained low in sustained responders.

Methodological comments:
- *Allocation to treatment groups:* randomisation was centralised and stratified by geographic region and HCV genotype (1 vs non-1). Patient identification numbers were allocated sequentially according to the order of enrolment. Patients were randomised in a 3:3:1 ratio (Group 1:Group 2:Group 3) to maximise the number of patients receiving treatment.
- *Allocation concealment*: central randomisation procedure – prepared and managed by ICTI (Lambertville, NJ, USA).
- *Blinding of outcome assessors:* HCV genotyping and HCV RNA qualitative and quantitative analyses were performed by the Nichols Institute (San Juan CA, USA) (blinding not specifically mentioned).
- *Analysis by ITT:* does not specifically state it is ITT analysis, but the analyses were carried out on all patients who received at least one dose of study medication and all untreated control patients with at least one post-baseline assessment. Patients without follow-up data were considered not to have achieved an SVR.
- *Comparability of treatment groups at pretreatment:* baseline characteristics were similar across the 3 groups. Statistical values were not presented.
- *Method of data analysis:* Pairwise comparisons among the 3 treatment groups were made using the Cochran–Mantel–Haenszel test stratified by geographic region and pretreatment HCV genotype. For the analysis of prognostic factors for SVR rates in treated patients, the SVR rates were based on a single HCV RNA determination during follow-up. Logistic regression and analysis of covariance were used to analyse categorical and continuous variables respectively.
- *Power analysis:* the study was designed to have 80% power to detect an increase in the SVR rate from 5% in the untreated control group to 22–25% in either of the treated groups at a two-sided significance level of 0.05. Numbers of patients required were not reported.
- *Attrition/drop-out:* 19 patients were randomised but not treated (reasons given); 78 patients withdrew prematurely from treatment (reasons given). One patient randomised to control group was treated by mistake for 24 weeks, and so was included in Group 1 for efficacy and safety analysis. In Group 1, 191/219 (87%) completed 24 weeks of treatment, 190/219 (87%) completed 24 weeks of follow-up and 161/219 (74%) completed 48 weeks of follow-up; in Group 2; 181/221 (82%) completed 24 weeks of treatment, 152/221 (69%) completed 48 weeks of treatment and 148/221 (67%) completed 24 weeks of follow-up; in Group 3, 69/74 (93%) completed 24 weeks of observation, 69/74 (93%) completed 48 weeks of observation and 61/74 (82%) completed 72 weeks of observation.

General comments:
- *Generalisability:* patients would appear to be representative of patients with mild chronic HCV without other co-morbidities.
- Conflict of interests: Roche sponsored the study and was responsible for the collection and statistical analysis of the data.
- *Definitions:* PNALT, ALT activity ≤ the upper limit of normal (ULN) documented on at least 3 occasions, a minimum of 4 weeks apart, with at least one value obtained during the 42-day screening period and at least one value obtained 6–18 months before screening; SVR, undetectable serum HCV RNA by qualitative PCR at the end of the 24-week untreated follow-up period (in Groups 1 and 2).

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Unknown
6. Was the patient blinded?	Not applicable as trial was open-label
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analysis include an ITT analysis?	Adequate
9. Were losses to follow-up completely described?	Partial

Appendix 16

Lindsay and colleagues:[73] data extraction and critical appraisal

Reference and design	Intervention	Participants	Outcome measures
Lindsay *et al.*, 2001[73] **Trial design:** Multicentre, double-blind RCT **Country:** International **Sponsor:** Schering Plough Research Institute and University of Southern California	**Intervention 1:** *n* = 315 PEG 2b (s.c.): Dose: 0.5 μg/kg once weekly Duration: 48 weeks **Intervention 2:** *n* = 297 PEG 2b (s.c.): Dose: 1.0 μg/kg once weekly Duration: 48 weeks **Intervention 3:** *n* = 304 PEG 2b (s.c.): Dose: 1.5 μg/kg once weekly Duration: 48 weeks **Intervention 4:** *n* = 303 IFN 2b (s.c.): Dose: 3 MIU 3 times per week Duration: 48 weeks	**Total numbers involved:** 1224 randomised, 1219 analysed **Eligibility:** adult chronic hepatitis C patients not previously treated with IFN, detectable serum HCV RNA, biopsy findings (in preceding 1 year) consistent with a diagnosis of chronic hepatitis, abnormal ALT values at entry and at least once during the 6 months before screening, using effective contraception. In addition: haemoglobin ≥ 12 g/dl for females and ≥ 13 g/dl for males, white blood cell count ≥4000/mm^3, neutrophil count ≥ 1,800/mm^3, platelets ≥ 130,000/mm^3, α-fetoprotein within normal limits or ≤50 ng/ml and ultrasound negative for evidence of hepatocellular carcinoma within 3 months before screening **Recruitment:** 53 centres in the USA, Europe and Australia, between August 1997 and August 1999 **Exclusion criteria:** any other cause for liver disease (hepatitis B infection, haemochromatosis, α-1 anti-trypsin deficiency, Wilson disease, autoimmune hepatitis, alcohol-, drug- or obesity-induced liver disease, HIV infection, haemophilia, haemoglobinopathies, active substance abuse, any known pre-existing medical condition that could interfere with participation, pregnant or breastfeeding **Baseline measurements:** **Viral load,** serum HCV RNA, geometric mean copies (×10^6/ml): 3.4 Group 1, 3.3 Group 2, 3.0 Group 3, 3.7 Group 4 >2 million copies/mL serum, no. (%): 231 (73%) Group 1 225 (76%) Group 2 220 (72%) Group 3 227 (75%) Group 4 **Serum ALT,**[a] median (range), × ULN: 2.3 (0.6–15.9) Group 1 2.2 (1.0–11.4) Group 2 2.3 (0.5–9.7) Group 3 2.3 (0.7–10.9) Group 4 **Histology:** Classification system used: Knodell	**Primary outcomes:** SVR **Secondary outcomes:** • normalisation of ALT • improvement in liver histology **Length of follow up:** 24 weeks after completion of therapy

continued

Reference and design	Intervention	Participants	Outcome measures
		Fibrosis score, no. (%): F3 (bridging): 164 (13%) F4 (cirrhosis): 43 (4%) Mean Knodell score: I + II + III (inflammation): 6.9 IV (fibrosis): 1.4 Timing of liver biopsy: performed within the preceding year (or, if not, performed at baseline) **Genotypes, no. (%):** 1: 851 (70%) 2: 125 (10% 3: 200 (16%) Other: 43 (4%) **Gender, no.** (%): 770 male (63%), 449 female (37%) **Age (years), mean (range):** 43.1 (18–73) **Ethnic groups, no. (%):** Caucasian: 1109 (91%) **Mode of infection, no. (%):** Transfusion: 261 (21.4%) Parenteral: 588 (48.2%) Sporadic/other: 370 (30.4%) **Losses to follow-up:** of 1219 treated patients, 943 (77%) completed the 72-week study. Pre- and post-treatment liver biopsies were analysed in 744 (61%) patients **Compliance:** 5 patients were randomised but not treated; 106 (9%) discontinued treatment	

Outcome % with response (*n*)	PEG 2b 0.5 μg/kg	PEG 2b 1.0 μg/kg	PEG 2b 1.5 μg/kg	IFN 2b 3 MU
Virological response:				
End of treatment	33% (105/315)[d]	41% (121/297)[f]	49% (149/304)[f]	24% (73/303)
SVR at follow-up[b]	18% (57/315)[e]	25% (73/297)[f]	23% (71/304)[f]	12% (37/303)
Combined virological and biochemical response:				
End of treatment	25% (79/315)	31% (92/297)[g]	33% (100/304)[f]	20% (61/303)
SVR at follow-up[c]	17% (52/315)	24% (70/297)[f]	23% (69/304)[f]	12% (37/303)
SVR by genotype and baseline viral load:				
Genotype 1 (all treatment groups)	10% (12/211)	14% (28/199)	14% (31/223)	6% (14/217)
≤ 2 million copies	27% (14/52)	38% (16/42)	34% (19/56)	21% (10/48)
>2 million copies	5% (8/159)	8% (12/157)	7% (12/167)	2% (4/169)
Genotype 2 or 3 (all treatment groups)	35% (31/88)	47% (39/83)	49% (36/73)	28% (23/81)
≤ 2 million copies	58% (14/24)	62% (13/21)	68% (15/22)	36% (9/25)
>2 million copies	27% (17/64)	42% (26/62)	41% (21/51)	25% (14/56)
Genotype 4, 5 or 6 (all treatment groups)	20% (2/10)	31% (4/13)	60% (3/5)	0/4
≤ 2 million copies	33% (2/6)	50% (4/8)	75% (3/4)	0/2
>2 million copies	0/4	0/5	0/1	0/2
Histology (proportion with improvement)				
Inflammation (%)	49% (97/198)	50% (89/178)	48% (85/177)	47% (90/191)
Mean change	–1.5	–1.8	–1.5	–1.2

continued

Outcome % with response (*n*)	PEG 2b 0.5 μg/kg	PEG 2b 1.0 μg/kg	PEG 2b 1.5 μg/kg	IFN 2b 3 MU
Fibrosis (%)	20% (40/198)	19% (34/178)	15% (27/177)	13% (25/191)
Mean change	–0.1	0	0.1	0.1
Adverse events (%):				
Dose discontinuation for:				
Any adverse event	9	11	9	6
Dose reduction for:				
Any adverse event	9	14	19	6
Thrombocytopenia	2–3	2–3	2–3	0.3
Neutropenia	2–3	2–3	5	2–3
Specific adverse events (%)				
Headache	61	64	64	58
Fatigue	43	51	45	50
Chills	34	40	44	33
Fever	31	45	44	30
Myalgia	48	54	61	53
Musculoskeletal pain	19	28	20	22
Nausea	21	26	25	20
Anorexia	10	20	25	17
Irritability	19	18	17	24
Insomnia	17	23	20	23
Alopecia	20	22	34	22
Injection site inflammation	44	42	40	16

[a] 5 subjects had normal ALT levels at baseline, all had at least 1 abnormal ALT level before baseline.
[b] 95% CI for the difference in response rate: PEG 1.5 vs IFN (–0.172 to –0.051), PEG 1.0 vs IFN (–0.185 to –0.062), PEG 0.5 vs IFN (–0.115 to 0.002).
[c] 95% CI for the difference in response rate: PEG 1.5 vs IFN (–0.174 to 0.036), PEG 1.0 vs IFN (–0.183 to –0.044), PEG 0.5 vs IFN (–0.106 to 0.020).
[d] $p = 0.01$.
[e] $p = 0.04$.
[f] $p < 0.001$.
[g] $p = 0.002$ (all for comparison with IFN).

Additional results:

Virological and biochemical response

- The higher EOTR rate in patients treated with PEG 1.5 vs PEG 1.0 (49 vs 41%, $p = 0.049$) was largely the result of a significantly higher response rate in HCV genotype 1-infected patients (87/223, 39% vs 50/199, 25%, respectively, $p = 0.002$).
- Unlike the EOTR, there was not a dose response between the PEG 1.0 and PEG 1.5 groups for SVR, 25 and 23%, respectively). This was related to a significantly higher relapse rate in the HCV genotype 1 patients treated with PEG 1.5 compared with PEG 1.0, 66% (57/87) and 46% (23/50), respectively ($p = 0.025$), whereas the relapse rate among patients infected with genotypes 2 or 3 was similar, 36% (20/56) and 38% (24/63), respectively.
- Logistic regression analysis identified only 2 covariates associated with SVR: HCV genotype other than 1 and baseline HCV RNA levels of ≤2 million copies/ml serum, $p < 0.001$.
- In each treatment group, the likelihood of an SVR occurring was highest in patients whose first negative HCV RNA occurred at treatment week 4 (77–86%), compared with those in whom HCV RNA was first negative at treatment week 12 (32–52%), and those whose HCV RNA was first negative at treatment week 24 (13–20%). Nearly all patients who eventually became sustained responders had developed undetectable serum HCV RNA by treatment week 24 (93–100%).
- NPVs for treatment week 4 were 85 and 77%, for patients treated with PEG 1.0 and 1.5, respectively.
- PPVs at treatment week 4 were 84 and 90% for PEG 1.0 and 1.5, respectively.
- Sustained normal ALT values were a poor predictor of sustained HCV RNA loss. Among subjects with normal ALT values after 24 weeks of follow-up, SVRs occurred in 67, 68, 80 and 82% of patients treated with IFN, PEG 0.5, PEG 1.0 and PEG 1.5, respectively.

Histological response

- The proportions of subjects who showed an improvement in hepatic inflammation and fibrosis scores were higher among subjects who had a sustained response than among those who either relapsed or did not respond.

continued

Safety
- No new or unexpected adverse events specific to PEG 2b were reported.
- In all cases, the characteristics of the injection-site reaction were similar for both IFN and PEG: the event was generally mild, not treatment limiting, and characterised by localised erythema.

Methodological comments:
Allocation to treatment groups: patients were randomly assigned to 1 of 4 treatment groups. No further details.
Allocation concealment: not reported.
Blinding of outcome assessors: study double-blinded for all PEG doses. Assays performed by a central laboratory. Liver biopsies scored by a single blinded pathologist.
Analysis by ITT: does not specifically state that it was ITT analysis but efficacy assessments were obtained in all patients who were randomised and received at least 1 dose of study drug ($n = 1219$).
Comparability of treatment groups at pretreatment: baseline demographics and disease characteristics were generally comparable across all treatment groups. However, there was a higher proportion of patients with genotype 1 in the PEG 1.5 group (73%) than in the PEG 1.0 and 0.5 groups (67% in each, $p = 0.09$).
Method of data analysis: all statistical tests were two-sided with a 0.05 level of significance. The SVR for PEG vs IFN was calculated by the χ^2 test. Baseline characteristics were compared using Kruskal–Wallis test. Relation of baseline characteristics and treatment response evaluated by logistic regression.
Power analysis: not reported.
Attrition/drop-out: efficacy results were based on all patients receiving at least one dose. The number discontinuing treatment was reported, but not reasons. Overall, 23% of patients not completing the study was relatively high; the report states that discontinuation rates were comparable across all treatment groups.

General comments
Generalisability: patients seem representative of European patient populations with a high percentage of genotype 1 and high baseline HCV RNA levels.
Conflict of interests: supported in part by a research contract from Schering Plough Research Institute, Kenilworth, NJ, USA.
Definitions: SVR, loss of detectable serum HCV RNA (<100 copies/ml serum) 24 weeks after completion of therapy; biochemical response, normalisation of ALT values, expressed in relationship to the upper limit of normal (ULN); an 'improved' inflammatory score was defined as a decrease of ≥2 units relative to pretreatment; an 'improved' fibrosis score was defined as a decrease of ≥1 unit relative to pretreatment; EOTR, end of treatment virological response; NPV, the likelihood that an SVR would occur if HCV RNA was not detected; PPV, the likelihood that an SVR would not occur if HCV RNA was detected.

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Partial
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the patient blinded?	Adequate
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
8. Did the analysis include an ITT analysis?	Adequate
9. Were losses to follow-up completely described?	Partial

Appendix 17

Reddy and colleagues:[72] data extraction and critical appraisal

Reference and design	Intervention	Participants	Outcome measures
Reddy *et al.*, 2001[72] **Trial design:** Multicentre RCT (3 cohorts, open-label) **Country:** USA **Sponsor:** Hoffman-La Roche Ltd, Switzerland	**Intervention** 1: *n* = 33 IFN 2a (s.c.) Dose: 3 MU 3 times per week Duration: 48 weeks **Intervention 2:** *n* = 20, 20, 45, 41 PEG 2a (40 kDa) (s.c.): Dose: 45, 90, 180 or 270 μg once weekly Duration: 48 weeks Randomised in a 4:1 ratio	**Total numbers involved:** 159 patients randomised and analysed **Eligibility:** treatment-naïve patients with chronic hepatitis C without bridging fibrosis or cirrhosis, i.e. Ishak fibrosis score 3 or 4 (15 patients with bridging fibrosis inadvertently included), serum PNALT activity (2 occasions ≥ 14 days apart), a positive anti-HCV antibody, pretreatment liver biopsy consistent with chronic hepatitis C, detectable pretreatment HCV RNA **Recruitment:** multicentre, 3 successive cohorts with ascending doses of PEG 2a were recruited (45 or 90 μg of PEG vs IFN then 180 μg of PEG vs IFN then 270 μg of PEG vs IFN). Conducted between February 1997 and March 1999 **Exclusion criteria:** liver disease from causes other than chronic hepatitis C, white blood cell count $<1500/mm^3$, platelet count $<90,000/mm^3$, serum creatinine >1.5 times the ULN, history of pre-existing medical conditions such as severe psychiatric illness, retinopathy, neoplasm (active or likely to recur), seizure disorder, unstable thyroid dysfunction and cardiac or renal disease, currently pregnant or breastfeeding, alcohol/drug dependence within previous 12 months, therapy with systemic antineoplastic or immunomodulatory agents within the past 6 months, administration of antiviral or investigational compounds within the past 3 months **Baseline measurements:** **Viral load**, mean HCV RNA (± SD), $\times 10^6$ copies/ml: 3.1 (± 3.1) IFN 1.7 (± 1.6) PEG 45 1.2 (± 1.5) PEG 90 2.3 (± 2.0) PEG 180 2.8 (± 3.2) PEG 270 ALT, mean (±SD), U/l: 95 (± 47) IFN 111 (± 102) PEG 45 80 (± 27) PEG 90 98 (± 50) PEG 180 97 (± 35) PEG 270	**Primary outcomes:** SVR **Secondary outcomes:** • Sustained biochemical response at week 72 • Virological and biochemical responses at end of treatment (week 48) • Histological response **Length of follow-up:** 24 weeks post-treatment

continued

Reference and design	Intervention	Participants	Outcome measures
		Histology: Classification system used: Ishak Fibrosis score, no. (%): Non-cirrhosis (≤F2): 144 (91%) Bridging fibrosis (F3): 15 (9%) HAI score, mean: 10.8 IFN, 11.7 PEG 45, 10.6 PEG 90, 10.7 PEG 180, 10.0 PEG 270 Timing of liver biopsy: obtained within 12 months before study treatment **Genotypes, no. (%):** 1: 73.6% Non-1: 23.9% Missing: 2.5% **Gender, no. (%):** 125 male (79%), 34 female (21%) **Age (years), mean (± SD):** 41.8 (± 5.9) IFN 41.9 (± 4.8) PEG 45 43.1 (± 6.7) PEG 90 42.0 (± 6.4) PEG 180 41.6 (± 5.7) PEG 270 **Ethnic groups, no. (%):** White: 139 (87%) Black: 14 (9%) Oriental: 2 (1%) Other: 4 (3%) **Mode of infection, no. (%):** not reported **Losses to follow up:** 122 completed 48 weeks of treatment; 23 were withdrawn due to adverse events **Compliance:** not reported	

Outcome % with response (*n*)	**IFN 2a 3 MIU**	**PEG 2a 45 μg**	**PEG 2a, 90 μg**	**PEG 2a- 180 μg**	**PEG 2a 270 μg**
Virological response:					
End of treatment	12% (4/33)	30% (6/20)	45% (9/20)[a]	60% (27/45)[b]	56% (23/41)[b]
SVR at follow-up	3% (1/33)	10% (2/20)	30% (6/20)[a]	36% (16/45)[b]	29% (12/41)[c]
SVR by genotype:					
1	4% (1/25)	7% (1/15)	14% (2/14)	31% (11/35)	12% (3/26)
Non-1	0 (0/4)	20% (1/5)	67% (4/6)	50% (5/10)	67% (8/12)
Biochemical response:					
End of treatment	15% (5/33)	20% (4/20)	20% (4/20)	38% (17/45)[d]	27% (11/41)
End of follow-up	9% (3/33)	10% (2/20)	25% (5/20)	38% (17/45)[c]	27% (11/41)
Histology (in patients with paired pre- and post-treatment biopsies):	(*n* = 23)	(*n* = 15)	(*n* = 17)	(*n* = 30)	(*n* = 29)
Change from baseline mean total: HAI score (± SEM)	–2.0 ± 0.6	–0.9 ± 0.8	–2.6 ± 1.0	–2.8 ± 0.6	–2.5 ± 0.7
Change from baseline median total: HAI score-2	–2.0	–1.0	–2.0	–3.0	–2.0
Proportion of histological responders, % (no.)	57% (13/23)	47% (7/15)	59% (10/17)	63% (19/30)	66% (19/29)

continued

Outcome % with response (*n*)	IFN 2a 3 MIU	PEG 2a 45 μg	PEG 2a, 90 μg	PEG 2a- 180 μg	PEG 2a 270 μg
Adverse events (%):					
Severe adverse events	10	7	2	10	7
Withdrawn for adverse events or laboratory abnormalities	9	10	0	22	20
Dose reduction for any adverse event					49 (20/41)
Specific adverse events, no. (%)[e]					
Fatigue	21 (70%)	14 (70%)	17 (85%)	30 (67%)	28 (70%)
Headache	18 (60%)	8 (40%)	7 (35%)	26 (58%)	19 (48%)
Myalgia	19 (63%)	8 (40%)	13 (65%)	14 (31%)	19 (48%)
Rigors	14 (47%)	1 (5%)	4 (20%)	21 (47%)	20 (50%)
Nausea	14 (47%)	9 (45%)	3 (15%)	20 (44%)	12 (30%)
Depression	3 (10%)	6 (30%)	7 (35%)	12 (27%)	15 (38%)
Diarrhoea	6 (20%)	5 (25%)	5 (25%)	14 (31%)	13 (33%)
Irritability	4 (13%)	7 (35%)	4 (20%)	13 (29%)	13 (33%)
Injection-site inflammation	6 (20%)	7 (35%)	6 (30%)	11 (24%)	10 (25%)
Insomnia	7 (23%)	5 (25%)	1 (5%)	15 (33%)	12 (30%)
Arthralgia	7 (23%)	4 (20%)	8 (40%)	8 (18%)	12 (30%)
Pyrexia	9 (30%)	3 (15%)	2 (10%)	11 (24%)	11 (28%)
Alopecia	6 (20%)	1 (5%)	6 (30%)	10 (22%)	10 (25%)
Upper abdominal pain	5 (17%)	6 (30%)	2 (10%)	8 (18%)	11 (28%)

[a] $p \leq 0.01$.
[b] $p < 0.001$.
[c] $p < 0.005$.
[d] $p < 0.05$.
[e] Events observed in at least 10% of patients; adverse events which occurred in ≥30% of patients in at least one study group are listed.

Additional results:

- SVR increased in a dose-dependent manner between 45 and 180 μg PEG with no further increase in response at the 270-μg dose.
- Most patients (94/159) who achieved a virological response did so within the first 16 weeks of treatment, particularly those in the 180- and 270-μg dose groups (78 and 73%, respectively).
- Of the patients with paired biopsies who achieved sustained virological responses, all but 2 (in 270-μg group) also achieved histological responses.
- Among the 88 patients with paired biopsies who did not have an SVR, between 42 and 60% in the PEG groups and 55% in the IFN group achieved a histological response.
- Depression, pruritis and irritability were reported in a higher percentage of patients in the PEG groups compared with the IFN group.
- Treatment with PEG was associated with mild, dose-dependent decreases in haemoglobin (<12 g/dl), but median haemoglobin concentrations remained within the normal range throughout the treatment period and no patients discontinued because of anaemia.

Methodological comments:

Allocation to treatment groups: randomised within 3 cohorts in which patients were assigned to 45 or 90 μg PEG or IFN (cohort 1), 180 μg PEG or IFN (cohort 2) and 270 μg PEG or IFN (cohort 3). Initial safety data (8 weeks) were reviewed by an independent safety review board for each cohort before successive cohorts were randomised to higher doses of PEG. Open-label trial.
Allocation concealment: not reported
Blinding of outcome assessors: open-label. Virological and biochemical assays were performed at a central laboratory. Histological response evaluated by a central pathologist in a coded, blinded fashion.
Analysis by ITT: efficacy analyses included all randomised patients, including 4 patients who were not treated. Safety analyses included all patients who received at least 1 dose of study medication and had at least 1 post-baseline safety assessment.
Comparability of treatment groups at pretreatment: Statistical comparisons were not reported. IFN group had the highest proportion of patients with genotype 1, a higher mean HCV RNA concentration and more patients with bridging fibrosis. This group also had more non-white patients.

continued

Method of data analysis: Fisher's exact test was used to compare biochemical, virological and histological responses between PEG and IFN groups.
Power analysis: not reported
Attrition/drop-out: 23% of randomised patients did not complete 48 weeks of treatment. There was no information as to whether these were equally distributed between treatment groups. 23 patients (14.4%) were prematurely withdrawn from the trial due to adverse events. Withdrawals due to adverse events were higher in the 180- and 270-μg PEG groups than the other treatment groups.

General comments
Generalisability: Patients seem representative of those with chronic hepatitis C without severe liver disease (no cirrhosis or bridging fibrosis) or other co-morbidities.
Conflict of interests: One author employed by Hoffmann-LaRoche, Inc.
Other: This is an ascending-dose trial to establish the most appropriate dose of PEG for subsequent, larger trials.
Definitions: SVR, proportion of patients with <100 copies/ml HCV RNA at week 72; biochemical response, normalisation of serum ALT activity; histological response, a ≥2-point decrease in the total histological activity index (HAI) between biopsies obtained at baseline and week 72 as determined by a pathologist.

Quality criteria (NHS CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Partial
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the patient blinded?	Not applicable as open-label trial
7. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
8. Did the analysis include an ITT analysis?	Adequate
9. Were losses to follow-up completely described?	Partial

Appendix 18

Bennett and colleagues:[88] economic evaluation data extraction and critical appraisal

Reference
Bennett and colleagues, 1997[88]

Study characteristics

Research question
What are the stated objectives of the evaluation?
To estimate the cost-effectiveness of IFN 2b in mild chronic hepatitis C.
More specifically, to determine whether treatment of histologically mild chronic hepatitis C with a single 6-month course of IFN 2b would affect life expectancy and lifelong costs.

Study population
What definition was used for mild chronic hepatitis C?
No specific definition of mild chronic hepatitis C was provided. The paper states, however, that hepatitis C virus chronically infects 3.9 million persons in the USA and is the most common cause of chronic liver disease.

What are the characteristics of the baseline cohort for the evaluation?

Age	One 35-year-old patient.
Sex	Unknown.
Race (if appropriate)	Unknown.
Genotype	Unknown.
Other characteristics	Presenting with histologically mild chronic hepatitis C.

Interventions and comparators
What number of interventions/strategies were included?
The model assumed a single 6-month course of recombinant IFN 2b.

Was a no treatment/supportive care strategy included?
There was not a no treatment/supportive care strategy included.

Describe interventions/strategies.
Intervention/strategy 1:
The five clinical trials included were selected because they all used the same treatment regimen (recombinant IFN 2b at a fixed dose of 3 MU administered three times weekly for 6 months), had systematic follow-up after treatment and had liver biopsy slides and study databases available for review. All patients were positive for antibody to HCV and had no evidence of coexisting liver diseases.

Analytical perspective
What is the perspective adopted for the evaluation (health service, health and personal social services, third-party payer, societal, i.e. including costs borne by individuals and lost productivity)?
A managed care perspective was used, as well as variable cost estimates (the amount spent by the hospital to care for one additional patient with the illness) based on individual variable cost estimates for actual patients with hepatitis C-related hospitalisations, including hospital and physician costs of the University of Florida.

Study type
Cost-effectiveness/cost-utility/cost–benefit analysis?
Cost-effectiveness analysis.

Institutional setting
Where is/are the intervention(s) being evaluated usually provided?
Hospital setting.

Country/currency
Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?
Results were primarily developed from US and European studies. Costs are expressed in $US. Results may not therefore be generalisable to East Asia, Africa, the Middle East and Australia, where HCV disease progression and response to IFN 2b may differ. The publication does not provide information on the base year to which the costs relate.

Data sources

Effectiveness
Were the effectiveness data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single study		
a review/synthesis or combination of previous studies	✓	Data was taken from five prospective trials and cost-effectiveness analyses. References for these studies are provided
expert opinion		

Give the definition of treatment effect used in the evaluation.
Treatment responses were determined according to baseline histological findings by reanalysis of the pooled data from five clinical trials involving 287 patients with chronic hepatitis. Traditional definitions of response were used. Persons with no response had ALT levels that did not return to normal by the end of treatment, persons with an end-of-treatment response had an unsustained normalisation of the serum ALT level and persons with a sustained response had a persistently normal serum ALT level for at least 6 months after completion of therapy.

Give the size of treatment effect used in the evaluation [include values used for subgroups (if applicable). Indicate the source for individual treatment effects (if appropriate)].
An end-of-treatment response occurred in 64% of patients with mild or moderate chronic hepatitis without fibrosis, 42% of those with chronic hepatitis with fibrosis and 28% of those with cirrhosis. A sustained response occurred in 31% of those with mild or moderate hepatitis, 11% of those with chronic hepatitis with fibrosis and 9% of those with cirrhosis.

Intervention costs
Were the cost data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study		
a review/synthesis or combination of previous studies	✓	Data were taken from five prospective trials and cost-effectiveness analyses. References for these studies are provided
expert opinion		

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used [indicate the source for individual cost values (if appropriate)].
Drug costs based on standard dosage (3 MU three times per week) and wholesale prices. Plus cost of counselling, laboratory tests and HCV RNA testing – frequency of contacts from treatment protocol.

Other direct costs (costs incurred directly in treating patients)
Were the cost data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study	✓	
a review/synthesis or combination of previous studies		
expert opinion	✓	

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used [indicate the source for individual cost values (if appropriate)].
Inpatient cost estimates were derived from patient data for hepatitis C-related hospitalisations at the University of Florida. Outpatient contacts, laboratory tests, radiography and drug use for each health state per year were estimated by a panel of hepatologists.

Indirect costs (costs due to lost productivity, unpaid inputs to patient care)
Were indirect costs included?
No indirect costs were included.

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued) [indicate the source for individual cost values (if appropriate)].
Not applicable.

Health state valuations/utilities (if study uses quality of life adjustments to outcomes)
Were the utility data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study		
a review/ synthesis or combination of previous studies		
expert opinion	✓	No patient surveys were available. Therefore, a panel of hepatologists were asked to use linear scaling and TTO methods to estimate the quality of life or utility for each health state on a scale of 0 (death) to 10 (perfect health)

List the utility values used in the evaluation [indicate the source for individual cost values (if appropriate)].
Refer to Table 3: quality-of-life adjustments – based on expert opinion

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation).
A decision analytic model using a Markov simulation was used.

Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.
This was a newly developed model. Because data on the natural history of hepatitis C are recent and somewhat uncertain, the validity of the analysis was tested by comparing model predictions with findings from published studies.

What was the purpose of the model (i.e. why was a model required in this evaluation)?
Given the lack of controlled clinical trials on the effect of interferon therapy in patients with mild chronic hepatitis C, the modest long-term response rate to interferon, and the many years usually required before disease complications arise, a decision analytic model was developed.

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported? – list them if reported.
Hypothetical cohorts of identical patients with histologically mild chronic hepatitis move through states of health defined by clinical and histologic descriptors. Time is represented by annual cycles during which patients may remain in the same histological or clinical state; progress or regress to another histological or clinical state; die of liver disease; or die of other causes as a function of sex, race and attained age. The simulation was carried out in each cohort until all patients died of liver-related or other causes.
Certain assumptions of the modelled were described. These are as follows:

1. Assumed that patients with relapse are not retreated, and that their subsequent prognosis is identical with that of patients with no response.
2. Assumed that patients who lose HCV either spontaneously or as a result of treatment will not develop progressive liver disease.
3. Because data on the effect of extrahepatic complications of HCV infection on disease progression, morbidity, mortality and response to treatment are insufficient, the impact of these data could not be modelled.
4. The authors could not determine with accuracy the age-dependent rate of liver disease progression from published studies. Thus, age was excluded from the model.
5. The authors did not consider serial liver biopsies. Because it was assumed that no retreatment would be given, biopsy would not affect treatment and would only add cost and morbidity. Thus, although the model contains other histological states, these states remain unobserved clinically until patients develop decompensated liver disease.
6. Although the model permits liver transplantation for cirrhosis, it does not consider liver transplantation for hepatocellular carcinoma. After patients undergo liver transplantation, the authors did not consider decreased survival from recurrent hepatitis C or HCC because of inadequate data. This is a bias against IFN 2b.
7. Viral factors could not be considered, such as genotype, pretreatment level of viraemia, or presumed source of infection, in this model.

Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).
Refer to Table 2: annual rates of probability of disease progression in patients with chronic hepatitis C.

What is the model time horizon?
Annual cycles.

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?
Costs, wholesale prices or charges adjusted by a cost-to-charge ratio were used for all calculations.

Results/analysis

What measure(s) of benefit were reported in the evaluation?
Increase in life expectancy.

Provide a summary of the clinical outcome/benefits estimated for each intervention/strategy assessed in the evaluation.
In 27% of patients with mild chronic hepatitis C treated with IFN 2b for 6 months, serum ALT levels permanently returned to normal and viral status remained negative. The model estimated that IFN 2b treatment in this population should increase life expectancy by 3.1 years if given at 20 years of age, by 1.5 years at 35 years of age and by 22 days at 70 years of age.

Provide a summary of the costs estimated for each intervention/strategy assessed in the evaluation.
The cost of a 6-month course of IFN 2b at 3 MU three times weekly was $2150; this cost increased to $2511 after the addition of drug-induced costs of counselling patients, additional follow-up laboratory evaluations and visits. However, for patients who were unresponsive to IFN 2b and had treatment discontinued after 3 months, the cost was reduced to $1253.

Synthesis of costs and benefits – are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results:
The costs and outcomes are reported together. Discounted marginal cost-effectiveness ratios were $500 per year of life gained for patients treated at 20 years of age, $1900 at 35 years of age and $62,000 at 70 years of age.

Give results of any statistical analysis of the results of the evaluation.
No further statistical analysis reported.

Was any sensitivity analysis performed – if yes, what type(s) [i.e. deterministic (one-way, two-way, etc.) or probabilistic]?
Sensitivity analysis was performed due to the variation in published data and expert estimates. The paper examined the effect of varying all the values over a wide range to assess their effect on the results. The range used was identified using the 95% CIs, halved and doubled cost and data estimates, or the range from the literature (whichever was greatest). Wherever possible, estimates that biased against IFN 2b therapy were used.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?
Each model variable was varied over a wide range of possible values. These were: annual probability of mild hepatitis becoming moderate; moderate hepatitis becoming cirrhosis; probability of durable viral-negative response to IFN 2b and cost of IFN 2b. Only four variables (cost of IFN 2b, response to IFN 2b, rate of transition from mild chronic hepatitis to moderate chronic hepatitis and rate of transition from moderate chronic hepatitis to cirrhosis) changed the results significantly.

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?
Varying the long-term response rates and progression rates for mild and moderate chronic hepatitis to near zero in sensitivity analyses substantially affected the results. Ratios ranged from $31,000 for a 20-year-old patient to $640,000 for a 70-year-old patient.
The base-case analysis was biased against IFN 2b by excluding quality of life adjustments and using conservative discounted variable costs. When both quality of life adjustments and Diagnosis Related Groups (DRG) reimbursements were used, IFN 2b was cost saving for 20- and 35-year-old patients and had a discounted marginal cost-effectiveness ratio less than $5000 for all patients 45–70 years of age.

Conclusions/implications

Give a brief summary of the authors' conclusions from their analysis.
On the basis of the estimations in this mathematical model of the natural history of chronic hepatitis C, treating mild chronic hepatitis with IFN 2b should prolong life expectancy at a reasonable marginal cost per year of life gained, particularly in younger patients.

What are the implications of the evaluation for practice?
In the absence of a long-term clinical trial, the analysis suggests that a single 6-month course of IFN 2b for mild chronic hepatitis should increase life expectancy at an economically reasonable cost that falls below that of many well-accepted healthcare interventions, particularly for younger patients.

Appendix 19

Davis and colleagues:[90] economic evaluation data extraction and critical appraisal

Reference
Davis and colleagues, 1998[90]

Study characteristics

Research question
What are the stated objectives of the evaluation?
To utilise a previously reported and validated mathematical model and results of published clinical trials to determine whether the longer duration of IFN treatment, currently recommended for patients with chronic hepatitis C, results in an incremental gain in life expectancy and cost-effectiveness, as compared with either a 6-month course of IFN or no treatment, in patients with histologically mild chronic hepatitis C.

Study population
What definition was used for mild chronic hepatitis C?
The diagnosis of mild chronic hepatitis was defined as a Knodell periportal inflammation score of 0 or 1 without fibrosis or cirrhosis.

What are the characteristics of the baseline cohort for the evaluation?

Age	35-year-old patient.
Sex	Unknown.
Race (if appropriate)	Unknown.
Genotype	Unknown.
Other characteristics	Histologically mild hepatitis C.

Interventions and comparators
What number of interventions/strategies were included?
Two interventions were included.

Was a no treatment/supportive care strategy included?
There was no 'no treatment' strategy included.

Describe interventions/strategies.
Intervention/strategy 1: IFN 2b given for 6 months.

Intervention/strategy 2: IFN 2b given for 18–24 months.

Analytical perspective
What is the perspective adopted for the evaluation (health service, health and personal social services, third-party payer, societal, (i.e. including costs borne by individuals and lost productivity)?
A managed-care perspective was utilised.

Study type
Cost-effectiveness/cost-utility/cost–benefit analysis?
Cost-effectiveness analysis.

Institutional setting
Where is/are the intervention(s) being evaluated usually provided?
Hospital setting.

Country/currency
Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?
All costs were normalised to 1995 US$.

Data sources

Effectiveness
Were the effectiveness data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single study		
a review/synthesis or combination of previous studies	✓	Treatment outcomes were taken from two large multicentre trials of IFN 2b given for 6 months or 18–24 months
expert opinion		

Give the definition of treatment effect used in the evaluation.
A sustained response was defined as a persistently normal serum ALT level at the end of treatment and for at least 6 months after discontinuation of therapy.

Give the size of treatment effect used in the evaluation [include values used for sub-groups (if applicable). Indicate the source for individual treatment effects (if appropriate)].
Based on analysis of the pooled database from the two clinical studies, end-of-treatment response was obtained in 61.5 and 50.0% of patients with mild chronic hepatitis without fibrosis treated for 18–24 or 6 months, respectively.

Intervention costs
Were the cost data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study	✓	The wholesale cost of outpatient medications was based upon the 1995 Red Book.
a review/synthesis or combination of previous studies		
expert opinion		

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used [indicate the source for individual cost values (if appropriate)].
The cost of a 6-month course of IFN 2b at 3 MU thrice weekly was $2150 and for an 18-month course $6450. After including the drug-induced costs for counselling patients, additional follow-up laboratory tests and visits, the total cost for a course was increased by $364 for each 6 months of therapy.

Other direct costs (costs incurred directly in treating patients)
Were the cost data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study	✓	
a review/synthesis or combination of previous studies		
expert opinion	✓	

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used [indicate the source for individual cost values (if appropriate)].
Based on values reported by Bennett and colleagues.[88]

Indirect costs (costs due to lost productivity, unpaid inputs to patient care)
Were indirect costs included?
No indirect costs were included.

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued) [indicate the source for individual cost values (if appropriate)].
Not applicable.

Health state valuations/utilities (if study uses quality of life adjustments to outcomes)
Were the utility data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study		
a review/synthesis or combination of previous studies	✓	Quality of life adjustments were used as described by Bennett and colleagues[88]
expert opinion		

List the utility values used in the evaluation [indicate the source for individual cost values (if appropriate)].
Based on values reported by Bennett and colleagues.[88]

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation).
A decision-analysis Markov model was used.

Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.
A slight modification of the decision-analysis model developed by Bennett and colleagues[88] was employed.

What was the purpose of the model (i.e. why was a model required in this evaluation)?
The model simulates disease progression and allows comparison of cohorts managed by observation alone or by IFN treatment.

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.
Hypothetical cohorts of identical patients with histologically mild chronic hepatitis move through health states defined by clinical and histological descriptors, e.g. mild hepatitis, compensated cirrhosis, death.

The rates of progression between these states were derived from the medical literature with interpretation and clarification by an expert panel of hepatologists.
The assumptions of the decision analysis are those utilised by Bennett and colleagues.[88] These included the following:

1. For purposes of assessing the effect of long-term treatment, an 18-month course was assumed.
2. Sustained response was the only favourable response considered. All other patients were considered to be non-responders.
3. Non-responders after the first 12 weeks of treatment stopped IFN because a favourable end of treatment response would be highly unlikely in such patients.
4. Relapse was not retreated in this model. Thus, the subsequent prognosis of patients who relapsed was assumed, for purposes of the model, to be identical with the pretreatment prognosis of that histological state of disease.
5. It was assumed that the presence of HCV was an essential requirement for disease progression. Thus, it was assumed that patients who eradicated HCV, either spontaneously or as a result of treatment, did not develop progression of their liver disease. For purposes of the model, patients with a sustained biochemical and virological response were assumed to have a lifelong cure.
6. The effect of age on the rate of liver disease progression could not be determined with certainty from published studies and therefore was not included. However, as preliminary reports suggest that histological progression may be accelerated in patients over the age of 55 years, exclusion of age from the model biases against treatment in older patients.
7. The effects of viral factors, such as genotype and the pretreatment level of viraemia, were not considered in the model.
8. Serial liver biopsies were not considered in the Bennett model. Thus, although the model describes the potential histological progression, this progression is not observed clinically so the cost of follow-up was assumed to be that of mild chronic hepatitis until subjects were found to be virus negative or presented with decompensated liver disease.

Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).
Based on values reported by Bennett and colleagues.[88]

What is the model time horizon?
Time was represented by annual cycles during which patients might remain in the same histological or clinical state, progress or regress to another histological or clinical state, die from liver disease or die from other causes based on gender, race and attained age.

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?
Hospital costs or adjusted (reduced) charges were used, rather than patient charges, to eliminate regional differences and economic biases that would favour treatment (by making the cost of disease appear greater). Whenever there was a discrepancy for cost (e.g. between actual hospital costs and published costs), the lesser figure was utilised.

Results/analysis

What measure(s) of benefit were reported in the evaluation?
Increase in life expectancy and quality-adjusted life expectancy.

Provide a summary of the clinical outcome/benefits estimated for each intervention/strategy assessed in the evaluation.
Based on analysis of the pooled database from the two clinical studies, end of treatment response was obtained in 61.5 and 50.0% of patients with mild chronic hepatitis without fibrosis treated for 18–24 or 6 months, respectively. Sustained response was achieved in 42.3 and 17.3% for 18–24 or 6 months, respectively. After discounting by 14% to estimate the virological relapse, the sustained viral-negative response rate for mild chronic hepatitis was 36.4% for 18–24 months of treatment and 15.3% for a 6-month course.

Provide a summary of the costs estimated for each intervention/strategy assessed in the evaluation.
The wholesale cost of outpatient medications was based on the 1995 Red Book. The cost of a 6-month course of IFN 2b at 3 MU thrice weekly was $2150 and for an 18-month course $6450. After including the drug-induced costs for counselling patients, additional follow-up laboratory blood tests and visits, the total cost for a course was increased by $364 for each 6 months of therapy. The model mandated discontinuation of IFN therapy in patients failing to respond to treatment by 3 months and therefore the cost was reduced in these patients to $1257. In patients aged 20–50 years, the discounted marginal cost per year of life gained by long-term IFN treatment ranged from $735 to $8856, and the gain in life expectancy ranged from 4.35 to 0.75 years, respectively, compared with an untreated age-matched cohort. Compared with treatment and healthcare costs, sustained response rates and the rate of progression during early disease were identified as significant variables in sensitivity analysis.

Synthesis of costs and benefits – are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.
0.98 QALY gain from 6 months and 2.26 QALY gain from 18–24 months of treatment. Incremental lifetime cost of $609 (6 months) and $1732 (18–24 months) for IFN 2b treatment compared with standard care.

Give results of any statistical analysis of the results of the evaluation.
Not applicable.

Was any sensitivity analysis performed – if yes, what type(s) [i.e. deterministic (one-way, two-way, etc.) or probabilistic]?
Owing to the variation in published data and expert estimates, all cost and progression rates were varied over a wide range to assess their effect on the results of the analysis. Wherever appropriate, in the base case or in sensitivity analysis, estimates that biased against IFN therapy were used.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?
Each variable in the model was tested over a wide range of possible values.

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?
For treatment response, the sensitivity analysis included a sustained viral-negative response, ranging from 10 to 40%, for 6 months of treatment. The analysis included a sustained viral-negative response for 18 months of treatment, which ranged from 15.3 to 50%. The viral clearance probabilities with 6 and 18 months of therapy varied simultaneously in a linked sensitivity analysis. In another sensitivity analysis, the cost of IFN was varied from 50 to 150% of baseline.

Conclusions/implications

Give a brief summary of the authors' conclusions from their analysis.
The treatment and healthcare costs, sustained response rates and the rate of progression during early disease were identified as significant variables in sensitivity analyses. Longer treatment always showed a survival benefit compared with 6 months of IFN or no treatment, and the cost of longer treatment is reasonable compared with that for a 6-month course.

Appendix 20

Wong and Koff:[92] economic evaluation data extraction and critical appraisal

Reference
Wong and Koff, 2000[92]

Study characteristics

Research question
What are the stated objectives of the evaluation?
To compare no antiviral treatment, periodic liver biopsy with subsequent antiviral treatment for moderate hepatitis or cirrhosis, and immediate antiviral therapy.

Study population
What definition was used for mild chronic hepatitis C?
Patients had elevated levels of serum aminotransferase, known genotype and liver biopsy revealing histologically mild liver inflammation (defined as Knodell periportal inflammation scores of 0–1).

What are the characteristics of the baseline cohort for the evaluation?

Age	Mean age 40.1 ± 8.9 years
Sex	Female (%) 34.6 ± 0.1%
Race (if appropriate)	
Genotype	Genotype 2 or 3 31.7 ± 0.1%
Other characteristics	See Table 1: baseline data

Interventions and comparators
What number of interventions/strategies were included?
The authors compared the risks and benefits of periodic biopsy with antiviral treatment alone by considering four strategies.

Was a no treatment/supportive care strategy included?
Natural history with no antiviral treatment was included.

Describe interventions/strategies
Intervention/strategy 1: natural history with no antiviral treatment.

Intervention/strategy 2: watchful waiting with liver biopsy every 3 years and combination therapy in patients found to have cirrhosis on liver biopsy.

Intervention/strategy 3: watchful waiting with liver biopsy every 3 years and combination therapy in patients found to have moderate hepatitis on liver biopsy.

Intervention/strategy 4: immediate empirical combination therapy.

Treatment consisted of combination therapy for 24 weeks in patients with genotype 2 or 3 and liver biopsy showing no cirrhosis. All other patients received combination therapy for 48 weeks, but treatment was discontinued in patients who had not responded at 24 weeks.

Analytical perspective
What is the perspective adopted for the evaluation (health service, health and personal social services, third-party payer, societal, i.e. including costs borne by individuals and lost productivity)?
Societal perspective, assuming that quality of life adjustments considered time or indirect costs.

Study type
Cost-effectiveness/cost–utility/cost–benefit analysis?
Cost-effectiveness analysis?

Institutional setting
Where is/are the intervention(s) being evaluated usually provided?
Hospital setting.

Country/currency
Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?
All costs were inflated from 1995 to 1998 US$ by using the Medical Care component of the Consumer Price Index.

Data sources

Effectiveness
Were the effectiveness data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single study		
a review/synthesis or combination of previous studies	✓	Clinical trial data and published studies (two large clinical trials)
expert opinion		

Give the definition of treatment effect used in the evaluation.
SVR.

Give the size of treatment effect used in the evaluation [include values used for subgroups (if applicable). Indicate the source for individual treatment effects (if appropriate)].
71.6% for women with genotype 2/3 and 36.7% for non-genotype 2/3.
62.5% for men with genotype 2/3 and 27.7% for non-genotype 2/3.

Intervention costs
Were the cost data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study	✓	
a review/synthesis or combination of previous studies		
expert opinion		

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used [indicate the source for individual cost values (if appropriate)].
Antiviral drug costs were based on average wholesale costs of $6.20 for 200 mg ribavirin and $11.64 per MU of interferon, but were adjusted for the actual drug dose received in the trial, which reflected patient

weight, dose reduction due to side-effects and drug discontinuation in patients who tested positive for HCV after 24 weeks of therapy.

Also included clinic visits, laboratory testing (electrolytes, blood counts and liver and thyroid tests), adverse events, pregnancy tests and contraception and abortion costs associated with ribavirin – basis for resource use or unit costs not stated.

Other direct costs (costs incurred directly in treating patients)
Were the cost data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study		
a review/synthesis or combination of previous studies	✓	Post-treatment costs were based on previously published actual variable costs, wholesale drug costs and charges adjusted with cost to charge ratios for patients with hepatitis C
expert opinion		

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used [indicate the source for individual cost values (if appropriate)].
Based on values reported by Bennett and colleagues[88] updated using appropriate pay and prices indices.

Indirect costs (costs due to lost productivity, unpaid inputs to patient care)
Were indirect costs included?
No indirect costs included.

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued) [indicate the source for individual cost values (if appropriate)].
Not applicable.

Health state valuations/utilities (if study uses quality of life adjustments to outcomes)
Were the utility data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study		
a review/synthesis or combination of previous studies		
expert opinion	✓	To reflect the morbidity associated with some states of health, life expectancy for quality of life was adjusted on a scale from 0 (dead) to 1 (perfect health) on the basis of assessments by an expert panel of senior hepatologists familiar with treatment and liver disease.

List the utility values used in the evaluation [indicate the source for individual cost values (if appropriate)].
See table 1: baseline data. Estimated using expert opinion, derived using the SG technique.

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation).
A decision analytic Markov model was used.
Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.
A previously described and validated Markov simulation model was used to estimate the long-term prognosis of each cohort with chronic hepatitis C.

What was the purpose of the model (i.e. why was a model required in this evaluation)?
The model was used to estimate the long-term prognosis of each cohort with chronic hepatitis C. The Markov model tracked cohort members as they moved through alternative states of health determined by clinical and histological descriptors.

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.
Within the model, patients may (1) remain in the same histological or clinical state; (2) progress to another histological or clinical state; (3) die of liver disease; (4) die of other causes based on sex, ethnicity and attained age; or (5) undergo liver biopsy. The simulations continued until all patients died.

Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).
See Table 1: baseline data. Based on values reported by Bennett and colleagues.[88]

What is the model time horizon?
Time was represented by annual cycles across the patients' lifetime.

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?
Because immediate combination therapy has higher current costs and its benefits occur in the future, discounting reduced the benefit of immediate therapy and increased its relative costs compared with future biopsy or no antiviral therapy. Immediate therapy increased lifetime discounted costs by $7000 and life expectancy by 1.0 discounted QALY, yielding a marginal cost-effectiveness ratio of $7000 per discounted QALY gained compared with no antiviral therapy. When discounted at 5%, this ratio increased to $13,500 per discounted QALY gained.

Results/analysis

What measure(s) of benefit were reported in the evaluation?
Increase in life expectancy and quality-adjusted life expectancy.

Provide a summary of the clinical outcome/benefits estimated for each intervention/strategy assessed in the evaluation.
Cohort with mean age of 40, over 20 years strategy 4 (biopsy every 3 years and treat if cirrhotic) reduces cirrhosis to 18% compared with 28% no treatment and avoids treatment in 50% of cohort compared with strategy 2 (biopsy every 3 years and treat if moderate hepatitis).

Provide a summary of the costs estimated for each intervention/strategy assessed in the evaluation.
Although watchful waiting reduced costs of antiviral therapy by $3400, costs of biopsy reached $6200. After including the cost of potential future HCV related complications, the lifetime cost of biopsy management exceeded the lifetime cost associated with immediate therapy by at least $5100. Because immediate therapy also prolonged life while reducing costs, it dominated biopsy management and was cost saving.
Post-treatment costs were based on previously published actual variable treatment costs, wholesale drug costs, and charges adjusted with cost to charge ratios for patients with hepatitis C.

Synthesis of costs and benefits – are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.
Incremental QALYs for strategies 2 and 4 vs no treatment are 1.1 and 0.6, respectively. Incremental costs are $7,000 and $6720.

Give results of any statistical analysis of the results of the evaluation.
Not applicable.

Was any sensitivity analysis performed – if yes, what type(s) [i.e. deterministic (one-way, two-way, etc.) or probabilistic)]?
One-way sensitivity analysis and Monte Carlo sensitivity analysis.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?
To examine the extent to which the results varied with alternative assumptions, additional analyses were performed for clinical subgroups. In addition, a Monte Carlo analysis was performed, in which all parameters are varied simultaneously over probability distributions defined by the 95% CIs or reasonable ranges. A unique set of random values was sampled for each variable (including patient characteristics, liver disease progression rates, treatment response rates and costs). For each unique set of values, the simulation projected the discounted quality-adjusted life expectancy and lifetime cost results for each strategy using four identical cohorts of 10,000 patients. These analyses were repeated 1000 times.

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?
Results of the one-way analysis are provided in Table 3. Results of the Monte Carlo sensitivity analysis are provided in Table 4.

Conclusions/implications

Give a brief summary of the authors' conclusions from their analysis.
For histologically mild chronic hepatitis C, initiation combination therapy compared with periodic liver biopsy should reduce the future risk of cirrhosis, prolong life and be cost-effective.

What are the implications of the evaluation for practice?
The analysis suggests that biopsy management would avoid treatment in many patients, especially over the next 20 years. Compared with immediate antiviral treatment, however, biopsy management permitted an increased cumulative incidence of cirrhosis and decreased survival.

Appendix 21

Grieve and Roberts:[93] economic evaluation data extraction and critical appraisal

Reference
Grieve and Roberts, 2002[93]

Study characteristics

Research question
What are the stated objectives of the evaluation?
To determine whether a combination of IFN and RBV is cost-effective for patients with mild HCV.

Study population
What definition was used for mild chronic hepatitis C?
No definition was provided for mild chronic hepatitis C.

What are the characteristics of the baseline cohort for the evaluation?

Age	40 years.
Sex	Not reported.
Race (if appropriate)	Not reported.
Genotype	Not reported.
Other characteristics	Mild HCV.

Interventions and comparators
What number of interventions/strategies were included?
IFN plus RBV was compared with no treatment.

Was a no treatment/supportive care strategy included?
A no treatment strategy was included.

Describe interventions/strategies
Intervention/strategy 1: IFN and RBV in the treatment of patients with HCV.

Intervention/strategy 2: No treatment.

Analytical perspective
What is the perspective adopted for the evaluation (health service, health and personal social services, third-party payer, societal, (i.e. including costs borne by individuals and lost productivity)?
Health service perspective (costs falling on social services, the patient and their carer were excluded from the analysis).

Study type
Cost-effectiveness/cost–utility/cost–benefit analysis?
Cost-effectiveness analysis.

Institutional setting
Where is/are the intervention(s) being evaluated usually provided?
Hospital/healthcare setting.

Country/currency
Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?
All costs were converted from UK pounds into euros using official exchange rates (£1 = 1.58 euros).

Data sources

Effectiveness
Were the effectiveness data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single study		
a review/synthesis or combination of previous studies	✓	A literature review was undertaken
expert opinion		

Give the definition of treatment effect used in the evaluation.
SVR.

Give the size of treatment effect used in the evaluation [include values used for subgroups (if applicable). Indicate the source for individual treatment effects (if appropriate)].
SVR of 43% for cohort containing genotype 1 and genotype non-1 patients (50:50 ratio). Same SVR for moderate as mild patients.

Intervention costs
Were the cost data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study		
a review/synthesis or combination of previous studies	✓	Model costs were taken from the literature
expert opinion		

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used [indicate the source for individual cost values (if appropriate)].
Table 2 presents the costs used in the model. Intervention costs based on Dusheiko and Roberts.[110]

Other direct costs (costs incurred directly in treating patients)
Were the cost data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study		
a review/synthesis or combination of previous studies	✓	
expert opinion		

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used [indicate the source for individual cost values (if appropriate)].
Table 2 presents the costs used in the model.Health state costs based on Dusheiko and Roberts[110] and Shepherd and colleagues.[87]

Indirect costs (costs due to lost productivity, unpaid inputs to patient care)
Were indirect costs included?
No indirect costs were included.

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued) [indicate the source for individual cost values (if appropriate)].
Not applicable.

Health state valuations/utilities (if study uses quality of life adjustments to outcomes)
Were the utility data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study		
a review/synthesis or combination of previous studies	✓	Values used were taken from the literature
expert opinion	✓	The estimates were derived by asking healthcare professionals to state the utility associated with being in the health states of interest.

List the utility values used in the evaluation [indicate the source for individual cost values (if appropriate)].
Table 2 states the costs and quality of life values used in the model. Based on Stein and colleagues.[94]

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation).
A Markov model was used.

Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.
The model structure was developed from the model previously outlined in Dusheiko and Roberts.[110] However, certain changes to the original structure were undertaken to take account of the aim of the model.

What was the purpose of the model (i.e. why was a model required in this evaluation)?
The aim of the model was to evaluate antiviral therapy for patients with mild rather than chronic HCV. Also, a separate substage was included for HCC.

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.
The model assumed that all cases were treated if they progressed to moderate disease or cirrhosis as recommended by UK guidelines.

Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).
A literature review was undertaken to find the best available estimates of disease progression rates for patients with HCV. Although there appeared to be a general consensus in the literature about the transition probabilities between later disease states, such as cirrhosis and decompensated cirrhosis, there was much less agreement about the rate of progression between mild and moderate disease. The

transition probabilities, which were felt to be most appropriate to the HCV population in the UK, were included in this version of the model. These are listed, along with their sources, in Table 1.

What is the model time horizon?
The model time horizon was not reported.

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?
All costs were discounted at 6% and outcomes at 1.5% as recommended by recent guidelines from the UK DoH (1998).

Results/analysis

What measure(s) of benefit were reported in the evaluation?
The results suggested that combined therapy for mild HCV is likely to prove a relatively cost-effective intervention. The projected cost per QALY for cases with mild HCV was €8490. This compares favourably with many other interventions which are routinely provided.

Provide a summary of the clinical outcome/benefits estimated for each intervention/strategy assessed in the evaluation.
The model predicted that on average, the intervention will mean 55 fewer deaths from liver disease for 1000 cases, which will lead to an average gain of 1.2 life-years. Apart from the reduction in mortality, CMB also reduced morbidity by preventing disease progression.

Provide a summary of the costs estimated for each intervention/strategy assessed in the evaluation.
The average lifetime costs for mild HCV were higher following treatment (€33,228) compared with no treatment for cases with HCV (€18,346). This is mainly because of the high treatment and monitoring costs associated with antiviral therapy for mild HCV (€21,534).
The ICER for the base case was €12,089 per life-year or €8490 per QALY.

Synthesis of costs and benefits – are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.
Measures of HRQoL were included for each of the health states included in the model. The ICER was calculated for CMB compared with no treatment.

Give results of any statistical analysis of the results of the evaluation.
Not applicable.

Was any sensitivity analysis performed – if yes, what type(s) [i.e. deterministic (one-way, two-way, etc.) or probabilistic)]?
Sensitivity analyses were run to examine the impact of changing assumptions on the progression rate and effectiveness of the intervention on the estimated cost-effectiveness of the intervention.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?
The sensitivity analysis looked at the impact of changing various parameters on the cost per QALY. These scenarios tested included subgroup genotype 1, subgroup genotype non-1, slow progression to cirrhosis and fast progression to cirrhosis.

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?
The analysis showed that the cost-effectiveness ratio varied widely according to certain parameters, e.g. for cases with genotype 1, the intervention was much less effective than for cases with genotype non-1 so the cost-effectiveness ratio was much higher. Similarly, for those patients who would progress from mild to moderate disease and then to cirrhosis at a fast rate (10% per year) without the intervention, then the cost-effectiveness ratio is more favourable than for those who would progress slowly through the illness.

Conclusions/implications

Give a brief summary of the authors' conclusions from their analysis.
These preliminary results suggest that CMB for mild HCV is likely to prove a relatively cost-effective intervention. The projected cost per QALY for cases with mild HCV was €8490. This compares favourably with many other interventions which are routinely provided.

What are the implications of the evaluation for practice?
Before results from the model are used to recommend that antiviral treatment should be provided for patients with mild HCV, certain concerns about the model need addressing.

Appendix 22

Saloman and colleagues:[91] economic evaluation data extraction and critical appraisal

Reference
Saloman *et al.*, 2003[91]

Study characteristics

Research question
What are the stated objectives of the evaluation?
To examine the clinical benefits and cost-effectiveness of newer treatments for chronic hepatitis C infection in a population of asymptomatic, HCV-seropositive but otherwise healthy individuals.

Study population
What definition was used for mild chronic hepatitis C?
Patients had elevated levels of ALT, positive results on quantitative HCV RNA assays and serological tests for antibody to HCV, and no histological evidence of fibrosis on liver biopsy.

What are the characteristics of the baseline cohort for the evaluation?

Age	40 years.
Sex	% female not reported.
Race (if appropriate)	Not applicable.
Genotype	% by genotype not reported.
Other characteristics	Baseline values are reported in Table 2.

Interventions and comparators
What number of interventions/strategies were included?
Five strategies for HCV infection were included.

Was a no treatment/supportive care strategy included?
A no treatment strategy was included.

Describe interventions/strategies
Intervention/strategy 1: no treatment
Intervention/strategy 2: monotherapy with IFN 2b
Intervention/strategy 3: monotherapy with PEG 2b
Intervention/strategy 4: combination therapy with IFN and RBV
Intervention/strategy 5: combination therapy with PEG and RBV.

Analytical perspective
What is the perspective adopted for the evaluation (health service, health and personal social services, third-party payer, societal, i.e. including costs borne by individuals and lost productivity)?
A societal perspective was adopted (although patient-time costs were excluded).

Study type
Cost-effectiveness/cost–utility/cost–benefit analysis?
The comparative efficiencies of alternative treatment strategies were measured by the incremental cost-effectiveness strategy.

Institutional setting
Where is/are the intervention(s) being evaluated usually provided?
Hospital setting.

Country/currency
Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?
Currency was presented in US$.

Data sources

Effectiveness
Were the effectiveness data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single study		
a review/synthesis or combination of previous studies	✓	Estimates for treatment efficacy were based on pooled results of randomised controlled trials. Presented in Table 2
expert opinion		

Give the definition of treatment effect used in the evaluation.
SVR.

Give the size of treatment effect used in the evaluation [include values used for subgroups (if applicable). Indicate the source for individual treatment effects (if appropriate)].
SVR of 31% for IFN dual therapy and 6% for monotherapy. SVR of 42% for PEG dual therapy and 15% for monotherapy in genotype 1.
SVR of 67% for IFN dual therapy and 26% for monotherapy and 79% for PEG dual therapy and 47% for monotherapy in genotype non-1.

Intervention costs
Were the cost data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study		
a review/synthesis or combination of previous studies	✓	Treatment costs were based on mean wholesale drug costs, combined with previously published cost estimates for clinic visits, laboratory tests and the treatment of adverse events
expert opinion		

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used [indicate the source for individual cost values (if appropriate)].
Table 2 presents the costs used in the model. Intervention costs based on Wong and colleagues.[136]

Other direct costs (costs incurred directly in treating patients)
Were the cost data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study	✓	Annual costs for patients in each of the clinical states in the model were derived from a published study that included detailed estimates of resource utilisation
a review/synthesis or combination of previous studies		
expert opinion		

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used [indicate the source for individual cost values (if appropriate)].
Based on values reported by Bennett and colleagues.[88]

Indirect costs (costs due to lost productivity, unpaid inputs to patient care)
Were indirect costs included?
No indirect costs were included.

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued) [indicate the source for individual cost values (if appropriate)].
Not applicable.

Health state valuations/utilities (if study uses quality of life adjustments to outcomes)
Were the utility data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study		
a review/synthesis or combination of previous studies	✓	For the base case analysis, previously published quality weights were applied to each health state
expert opinion		

List the utility values used in the evaluation [indicate the source for individual cost values (if appropriate)].
Table 2 presents HRQoL weight. Table 4 presents incremental costs per life-year and quality-adjusted life-year saved or combination therapy with PEG compared with standard IFN. Health state weights were taken from Wong and colleagues.[117]

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation).
A Markov model was developed.

Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.
The model was newly developed. Natural history parameter values in the model were derived from the authors' previous empirical calibration study.[109] Values for the additional parameters demanded by the more detailed structure of the model were derived from the empirically calibrated parameters (listed in Table 1), combined with other estimates from the literature.

What was the purpose of the model (i.e. why was a model required in this evaluation)?
The structure of the Markov model used in this decision analysis included a more detailed specification of the complications of cirrhosis than did the model used for empirical calibration to build on an existing body of cost-effectiveness work, including published data pertaining to annual costs of care for specific states of ascites, variceal haemorrhage and hepatic encephalopathy.

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.
To be consistent with current guidelines, it was assumed that: (1) monotherapy was administered for 48 weeks; (2) combination therapy was administered for 48 weeks in patients with HCV genotype 1 and 24 weeks in patients with all other HCV genotypes; (3) treatment was discontinued in patients with detectable HCV RNA levels after either 12 weeks of receiving monotherapy or 24 weeks of receiving combination therapy.

Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).
Transition probabilities determined the movements of patients through different health states until all members of the cohort had died. Each year, patients faced probabilities of fibrosis progression, complications from cirrhosis and competing mortality risks from decompensated cirrhosis, HCC and other causes unrelated to HCV infection.

What is the model time horizon?
Lifetime.

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?
All costs and clinical consequences were discounted at a rate of 3%.

Results/analysis

What measure(s) of benefit were reported in the evaluation?
Life expectancy and quality-adjusted life expectancy.

Provide a summary of the clinical outcome/benefits estimated for each intervention/strategy assessed in the evaluation.
Probability of developing cirrhosis over 30 years ranged from 13 to 46% in men and 1 to 29% in women.

Provide a summary of the costs estimated for each intervention/strategy assessed in the evaluation.
The incremental costs for each strategy ranged from $2000 to $4000, with incremental gains in life expectancy ranging from 1 to 2 months. IFN therapy was weakly dominated by PEG therapy, and the ICERs of the combination strategies were between $24,000 and $35,000 per QALY gained.

Synthesis of costs and benefits – are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.
ICERs for dual therapy with PEG ($26,000–64,000 for genotype 1 and $10,000–28,000 for genotype non-1 in men; $32,000–90,000 for genotype 1 and $12,000–42,000 for genotype non-1 in women). Benefits largely depend on improved quality of life, not survival.

Give results of any statistical analysis of the results of the evaluation.
Not applicable.

Was any sensitivity analysis performed – if yes, what type(s) [i.e. deterministic (one-way, two-way, etc.) or probabilistic]?
Sensitivity analysis was performed.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?
Sensitivity analyses were performed on costs, treatment efficacy and HRQoL.

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?
The results were insensitive to variation in annual costs or managing chronic hepatitis C or its complications and relatively insensitive to assumptions about the efficacy of different treatment regimens. If costs of a specific treatment regimen for HCV infection were to vary within a range of ±50%, the given strategy typically would be dominated or be dominated by adjacent strategies at the extreme values of the ranges. Results were sensitive to the discount rate used; with no discounting, the ICERs of all treatment strategies were all lower than in the base case by approximately 60–80%. Results were highly sensitive to plausible alternative assumptions about the impact of chronic HCV infection and treatment of quality of life. Results were also sensitive to alternative assumptions about the decrements of quality of life associated with treatment.

Conclusions/implications

Give a brief summary of the authors' conclusions from their analysis.
Although newer treatment options for hepatitis C appear to be reasonably cost-effective on average, these results vary widely across different patient subgroups and depend critically on quality of life assumptions.

What are the implications of the evaluation for practice?
As the pool of persons eligible for treatment for HCV infection expands to the more general population, it will be imperative for patients and their physicians to consider the assumptions from this study in making individual-level treatment levels.

Appendix 23

Grieve and colleagues:[12] economic evaluation data extraction and critical appraisal

Reference
Grieve and colleagues, 2005[12]

Study characteristics

Research question
What are the stated objectives of the evaluation?
To assess whether antiviral therapy (either IFN or PEG combined with RBV) is cost-effective at a mild stage compared with waiting and only treating those cases who progress to moderate disease.

Study population
What definition was used for mild chronic hepatitis C?
Patients with mild chronic hepatitis C.

What are the characteristics of the baseline cohort for the evaluation?

Age	40 years
Sex	60% male
Race (if appropriate)	–
Genotype	50% genotype 1
Other characteristics	–

Interventions and comparators
What number of interventions/strategies were included?
Four interventions were included.

Was a no treatment/supportive care strategy included?
A no treatment strategy was included.

Describe interventions/strategies.
Intervention/strategy 1: mild disease, no treatment; moderate disease, IFN 2b + RBV.

Intervention/strategy 2: mild disease, IFN 2b + RBV; moderate disease, no treatment.

Intervention/strategy 3: mild disease, no treatment; moderate disease, PEG 2b + RBV.

Intervention/strategy 4: mild disease, PEG 2b + RBV; moderate disease, no treatment,

Analytical perspective
What is the perspective adopted for the evaluation (health service, health and personal social services, third-party payer, societal, i.e. including costs borne by individuals and lost productivity)?
A health service perspective was taken to costing; the inpatient and outpatient costs incurred from hospital care were included.

Study type
Cost-effectiveness/cost–utility/cost–benefit analysis?
Cost-effectiveness study.

Institutional setting
Where is/are the intervention(s) being evaluated usually provided?
Hospital or liver clinics.

Country/currency
Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?
All costs were reported in 2002–3 prices (£), and the main cost results were converted into US$ using 2002–3 purchasing power parties to assist with the interpretation of results (OECD, 2004).

Data sources

Effectiveness
Were the effectiveness data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single study	✓	The effectiveness data for IFN 2b and ribavirin from a mild hepatitis C RCT were used as a basis for estimating the likely effectiveness of PEG 2b and RBV in routine clinical practice.
a review/synthesis or combination of previous studies		
expert opinion		

Give the definition of treatment effect used in the evaluation.
SVR.

Give the size of treatment effect used in the evaluation [include values used for sub-groups (if applicable). Indicate the source for individual treatment effects (if appropriate)].
SVR of 33% (18% genotype 1 and 49% genotype non-1) based on one clinical trial for IFN. SVR for PEG (24% genotype 1 and 55% genotype non-1), based on OR for SVR for PEG compared with IFN from one clinical trial.

Intervention costs
Were the cost data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study	✓	
a review/synthesis or combination of previous studies		
expert opinion		

List the direct intervention costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used [indicate the source for individual cost values (if appropriate)].
Total costs were calculated by multiplying each patient's resource use by the relevant unit cost. Unit costs were developed during clinical trial. Drug costs were adjusted by dose reductions and discontinuation observed in clinical trial.

Other direct costs (costs incurred directly in treating patients)
Were the cost data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study	✓	The costs of liver transplantation were taken from a UK study of the costs and outcomes following liver transplantation.[129]
a review/synthesis or combination of previous studies	✓	
expert opinion		

List the costs used in the evaluation – if quantities of resource use are reported separately from cost values, show sources for the resource estimates as well as sources for unit costs used [indicate the source for individual cost values (if appropriate)].
Health state costs were developed based on trial patients and an additional observational study conducted alongside trial.

Indirect costs (costs due to lost productivity, unpaid inputs to patient care)
Were indirect costs included?
No indirect costs were included.

Describe how indirect costs were estimated (e.g. how days of lost productivity were estimated and how those days were valued) [indicate the source for individual cost values (if appropriate)].
Not applicable.

Health state valuations/utilities (if study uses quality of life adjustments to outcomes)
Were the utility data derived from:

	Tick	*Were the methods for deriving these data adequately described (give sources if using data from other published studies)?*
a single (observational) study	✓	
a review/synthesis or combination of previous studies	✓	
expert opinion		

List the utility values used in the evaluation [indicate the source for individual cost values (if appropriate)].
Health state valuations were developed based on trial patients and an additional study conducted alongside trial. EQ-5D administered to trial patients pre- and post-treatment. Also administered to patients with SVR, cirrhosis and decompensation. Values for liver transplantation patients taken from Ratcliffe and colleagues.[128]

Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation).
A Markov model was used.

Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original.
The model's structure and main assumptions were similar to previous models for hepatitis C and have been described previously.[93]

What was the purpose of the model (i.e. why was a model required in this evaluation)?
The model was required to estimate the lifetime cost-effectiveness of antiviral treatment for patients with mild chronic hepatitis C.

What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.
The Markov model required the natural history of the disease to be divided into a series of health states. Two hypothetical cohorts with the characteristics of the UK mild hepatitis C trial population were entered into the model and faced annual probabilities of progression to subsequent health states. The cases in the 'treatment group' were all assumed to have antiviral therapy at a mild stage, with a proportion having an SVR and no longer facing a probability of progression. Patients in the 'no treatment group' did not receive treatment at a mild stage; those cases predicted by the model to reach moderate disease were assumed to have antiviral treatment in accordance with recent UK recommendations.

Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).
The transition probabilities for mild to moderate disease and moderate disease to cirrhosis were estimated by re-analysing data from UK cross-sectional and longitudinal datasets. Subsequent transition probabilities were taken from the literature. Annual transition probabilities are shown in Table 1. The transition probabilities were based on studies that recruited patients from a hospital rather than a community setting, in order to fit in with the perspective of the study. The transition probabilities used for progression from mild to moderate disease and moderate disease to cirrhosis were compared with estimates from a recent systematic review of progression rates in hepatitis C.[65] These were lower than those derived from other studies that recruited cases from liver clinics, but higher than estimates from community-based studies.

What is the model time horizon?
The model duration is up to 50 years, The duration of treatment for all patients is 52 weeks.

What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?
All estimates were discounted at a rate of 3.5%.

Results/analysis

What measure(s) of benefit were reported in the evaluation?
Life expectancy and quality-adjusted life expectancy.

Provide a summary of the clinical outcome/benefits estimated for each intervention/strategy assessed in the evaluation:
Genotype non-1 patients gain 0.61 QALYs with early treatment over delayed treatment. Lower QALY gain (0.18) for genotype 1 for early treatment.

Provide a summary of the costs estimated for each intervention/strategy assessed in the evaluation.
Unit costs for antiviral therapy and all other medication use were taken from the BNF. All other unit costs were collected from the finance departments at the three centres concerned.
Incremental lifetime cost of £2300 with IFN and incremental lifetime cost of £4000 with PEG.

Synthesis of costs and benefits – are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.
£3733/QALY for IFN 2b dual therapy for genotype non-1. ICER of £28,754 per QALY for PEG for genotype non-1. ICERs are £23,029/QALY for IFN 2b dual therapy and £36,440/QALY for PEG for genotype 1.

Give results of any statistical analysis of the results of the evaluation.
Not applicable.

Was any sensitivity analysis performed – if yes, what type(s) [i.e. deterministic (one-way, two-way, etc.) or probabilistic].
Multivariate Monte Carlo sensitivity analyses were used to consider the random variation across the input parameters and to report CEACs.

What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?
In further sensitivity analysis, certain assumptions made in the base case model were examined; the treatment duration was reduced to a maximum of 24 weeks for patients with genotype non-1 and to 12 weeks for patients identified as having insufficient change in viral load at week 12. The impact of assuming different levels of improvement in HRQoL and using a 30-year time horizon was also considered.

Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?
The finding that antiviral treatment at a mild stage was cost-effective (i.e. ICER less than £30,000 per QALY) for patients with genotype non-1 was deemed robust to alternative methodological assumptions. This was not the case for patients with genotype 1, if the gain in quality of life was reduced (or zero), if model time horizon reduced from 50 to 30 years or if transition probabilities for early progression were lower than for the base case, the ICER increased above £30,000. Using viral kinetics to target treatment according to early response and higher efficacy estimates reduced the ICER (to £15,815 and £12,125, respectively).

Conclusions/implications

Give a brief summary of the authors' conclusions from their analysis
For patients with chronic hepatitis C and genotype non-1, antiviral treatment compared with no treatment at a mild stage is cost-effective. For patients with genotype 1, antiviral therapy at a mild disease stage is not cost-effective.

What are the implications of the evaluation for practice?
For patients with mild chronic hepatitis C and genotype non-1, where treatment with IFN or PEG and RBV is cost-effective, liver biopsy prior to treatment is no longer justified. For patients with genotype 1, where early intervention is not cost-effective, monitoring by liver biopsy and providing PEG and RBV only to those cases that progress to moderate disease is the most cost-effective strategy.

Appendix 24

Costing protocols for patient evaluation and for monitoring during and after treatment

Evaluation of a new patient with confirmed HCV

Item		Per hour (£)	Cost (£)
Outpatient appointment:			
Time with nurse – 1 hour (Grade H assumed)		16.56	16.56
Time with doctor – 20 minutes (Consultant assumed)		46.35	15.45
Total staff time			32.01
Clinic administration (pulling notes, etc.)			3.58
Staff cost for outpatient appointment			35.59
Tests and investigations:			
Hepatitis C screen (HCV RNA)	Virology		11.33
HBV (for 50% of patients)	Virology		5.18
Liver function tests	Chemical pathology		3.60
α-Fetoprotein (cirrhotic patients – 15%)	Chemical pathology		1.31
α-Antitrypsin	Chemical pathology		5.50
Thyrotropin	Chemical pathology		3.60
Free T4	Chemical pathology		3.60
Full blood count	Haematology		2.20
Autoantibodies	Immunology		22.30
Immunoglobulins	Immunochemistry		2.20
Ferritin	Haematology		10.00
Caeruloplasmin	Chemical pathology		6.60
Iron	Chemical pathology		4.30
Urea and electrolytes (including renal profile and urea)	Chemical pathology		5.60
Blood clotting factors (INR)	Haematology		2.40
Glucose	Chemical pathology		2.50
FBC	Haematology		2.20
Ultrasound scan of liver	Radiology		48.00
Chest X-ray	Radiology		15.00
ECG			31.00
Cryoglobulin	Immunochemistry		11.90
Pulmonary function tests (estimated 5% of patients)			1.00
Total			236.90

Further investigations of a patient with HCV considered for treatment

Item		Per hour (£)	Cost (£)
Outpatient visit:			
To review results from above tests and brief on treatment options			
Time with nurse – 20 minutes (Grade H assumed)		16.56	5.52
Time with doctor - 20 minutes (Consultant assumed)		46.35	15.45
Clinic administration (pulling notes, etc.)			3.58
Staff cost for outpatient appointment			24.54
HCV quantitative PCR	Molecular pathology		152.27
HCV genotype	Not done at SUHT		148.00
Pregnancy test (estimated 5% of patients)	Chemical pathology		0.25
Daycase for liver biopsy:			
Additional tests undertaken prior to biopsy:			
FBC	Haematology		2.20
INR	Haematology		2.40
Blood group	Haematology		2.20
Ultrasound guided biopsy (by radiologists)	Radiology		173.00
Liver biopsy costs in pathology	Histopathology		126.00
Clerking in patient – 30 minutes (Grade D nurse assumed)		£10.18	5.09
Ward time for recovery post-biopsy – 6 hours			0.00
Additional costs for time on ward estimated at 10%			0.00
Total			**635.95**

Monitoring during active treatment with interferon alfa (24 weeks)

Item		Per hour (£)	Cost (£)
1st appointment:			
Time with nurse – 120 minutes (Grade H assumed)		16.56	33.13
Time with doctor – 10 minutes (Consultant assumed)		46.35	7.72
Clinic administration (pulling notes, etc.)			3.58
STAFF cost for outpatient appointment			44.43
FBC	Haematology		2.20
INR	Haematology		2.40
U&Es	Chemical pathology		5.60
LFT	Chemical pathology		3.60
HCV quantitative viral load	Molecular pathology		152.27
Pregnancy test (5% of patients)	Chemical pathology		0.25
Total for first treatment appointment			**210.74**
Subsequent appointments:			
Basic checks (at weeks 1, 2, 6, 16 and 20)			
Time with nurse – 30 minutes (Grade H assumed)		16.56	8.28
Time with doctor – 5 minutes (Consultant assumed)		46.35	3.86
Clinic administration (pulling notes, etc.)			3.58
Staff cost for appointment			15.72
FBC	Haematology		2.20
U&Es	Chemical pathology		5.60
LFT	Chemical pathology		3.60
Pregnancy test (week 16+20)			0.25
Total for each basic assessment			**27.36**

continued

Item		Per hour (£)	Cost (£)
Hence total cost for basic assessments			136.82
More detailed assessment (at weeks 4 and 8):			
Time with nurse – 30 minutes (Grade H assumed)		16.56	8.28
Time with doctor – 5 minutes (Consultant assumed)		46.35	3.86
Clinic administration (pulling notes, etc.)			3.58
Staff cost for appointment			15.72
FBC	Haematology		2.20
U&Es	Chemical pathology		5.60
LFT	Chemical pathology		3.60
INR	Haematology		2.40
Pregnancy test (5% of patients)	Chemical pathology		0.25
Total for 4- and 8-week assessment			**29.76**
Hence total cost for 4- and 8-week assessments			59.53
Detailed assessment (week 12):			
Time with nurse – 30 minutes (Grade H assumed)		16.56	8.28
Time with doctor – 10 minutes (Consultant assumed)		46.35	7.72
Clinic administration (pulling notes, etc.)			3.58
Staff cost for appointment			19.58
FBC	Haematology		2.20
U&Es	Chemical pathology		5.60
LFT	Chemical pathology		3.60
INR	Haematology		2.40
TFT (thyroid function tests)	Chemical pathology		13.30
AFP (cirrhotic patients – 15%)	Chemical pathology		1.31
HCV viral load	Molecular pathology		152.27
Pregnancy test (5% of patients)	Chemical pathology		0.25
Total cost for 12-week assessment			**200.50**
Detailed assessment (week 24):			
Time with nurse – 30 minutes (Grade H assumed)		16.56	8.28
Time with doctor – 15 minutes (Consultant assumed)		46.35	11.59
Clinic administration (pulling notes, etc.)			3.58
Staff cost for appointment			23.44
FBC	Haematology		2.20
U&Es	Chemical pathology		5.60
LFT	Chemical pathology		3.60
INR	Haematology		2.40
TFT	Chemical pathology		13.30
AFP	Chemical pathology		1.31
HCV RNA (qualitative)	Virology		11.33
Ultrasound of liver (cirrhotic patients only)	Radiology		7.20
Pregnancy test (5% of patients)	Chemical pathology		0.25
Total cost for 24-week assessment			**70.62**

Monitoring during interferon alfa treatment (48 weeks)

All patients would receive the treatments as per the 24-week patients

Item	Cost (£)
First appointment	210.74
Basic assessments (weeks 1, 2, 6, 16 and 20)	136.82
Week 4 and week 8 assessments	59.53
Week 12 assessment	200.50
Week 24 assessment	70.62
Total	678.21
Subsequent assessments: Weeks 28, 32, 40 and 44 (as basic assessments, plus pregnancy test) Per assessment	27.61
Total assessments	110.44
Week 36 (as week 12, excluding viral load)	48.23
Week 48 (as week 24)	70.62
Total monitoring cost for 48-week patient	**907.50**

Surveillance of patients failing, refusing or unsuitable for treatment (per year)

Item	Per hour (£)	Cost (£)
3 outpatient appointments:		
Staff costs – assumes 20 minutes per appointment with doctor or nurse (alternates – average cost is taken)	16.56 46.35	31.45
Alt 3 times per year:		10.80
Liver function tests		10.80
α-Fetoprotein 3 times per year:		3.92
INR (twice per year)		4.80
Tests for cirrhotic patients only (estimated 15% of patients):		
Liver ultrasound twice		14.40
Additional outpatient appointment (4 per year)		8.55
Total for year		**84.72**

[a] NB, commitment to caring for these patients will be long-term.

Surveillance of patients following response after 1 year of treatment completed (per year)

Item		Per hour (£)	Cost (£)
4 weeks post-treatment:			
Staff costs – assumes 20 minutes per appointment with doctor or nurse (alternates – average cost is taken)			10.48
Clinic administration			3.58
Total staff costs			14.06
FBC	Haematology		2.20
INR	Haematology		2.40
U&Es	Chemical pathology		5.60
LFT	Chemical pathology		3.60
Pregnancy test (5%)	Chemical pathology		0.25
Total			**28.10**
12 weeks post treatment:			
Staff costs – assumes 20 minutes per appointment with doctor or nurse (alternates – average cost is taken)			10.48
Clinic administration			3.58
Total staff costs			14.06
FBC	Haematology		2.20
U&Es	Chemical pathology		5.60
LFT	Chemical pathology		3.60
AFP	Chemical pathology		1.31
Pregnancy test (5%)	Chemical pathology		0.25
Total			**27.01**
24 weeks post-treatment:			
Staff costs – assumes 20 minutes per appointment with doctor or nurse (alternates – average cost is taken)			10.48
Clinic administration			3.58
Total staff costs			14.06
U&Es	Chem pathology		5.60
LFT	Chem pathology		3.60
HCV RNA	Virology		11.33
Ultrasound on liver	Radiology		48.00
AFP (cirrhotic patients)	Chemical pathology		1.31
Pregnancy test (5%)	Chemical pathology		0.25
Total			**84.14**
Total monitoring costs per year			139.25

Appendix 25

Variables and probability distributions used in the probabilistic model

Description	Distribution type, parameters and expected value
Transition probabilities (TPs)	
TP: mild to moderate chronic hepatitis C	β, α = 38.0859, β = 1485.3516; expected value: 0.025
TP: moderate chronic hepatitis C to compensated cirrhosis	β, α = 26.9050, β = 700.2582; expected value: 0.037
TP: cirrhosis to HCC	β, α = 1.9326, β = 136.1074; expected value: 0.014
TP: cirrhosis to decompensated disease	β, α = 14.6168, β = 360.1732; expected value: 0.039
TP: cause-specific excess mortality for decompensated disease	β, α = 147.0300, β = 983.9700; expected value: 0.13
TP: HCC excess mortality	β, α = 117.1033, β = 155.2300; expected value: 0.43
TP: decompensated cirrhosis to liver transplant	β, α = 6.5256, β = 210.9945; expected value: 0.03
TP: liver transplant to death	β, α = 16.2762, β = 61.2294; expected value: 0.21
TP: post-liver transplant to death	β, α = 22.9017, β = 378.8825; expected value: 0.057
Health state costs	
Cost of SVR state	γ, α = 28.8141, β = 8.9887; expected value: 259
Cost of mild chronic hepatitis C state	γ, α = 25.6995, β = 5.3698; expected value: 138.0011751
Cost of moderate chronic hepatitis C state	γ, α = 88.8502, β = 8.0698; expected value: 717
Cost of compensated cirrhosis state	γ, α = 24.2342, β = 46.9584; expected value: 1138
Cost of decompensated cirrhosis state	γ, α = 36.0249, β = 253.1582; expected value: 9120
Cost of HCC state	γ, α = 18.1081, β = 448.8045; expected value: 8127
Cost of liver transplant	γ, α = 89.7536, β = 304.5004; expected value: 27,330
Cost of care in year in which transplant occurs	γ, α = 13.7788, β = 686.4168; expected value: 9458
Cost of care in years after liver transplant occurs	γ, α = 15.2189, β = 91.0053; expected value: 1385
Health state utilities	
Utility of SVR (SVR from mild chronic hepatitis C health state)	β, α = 65.8678, β = 14.4588; expected value: 0.82
Utility of SVR (SVR from mild chronic hepatitis C health state)	β, α = 58.0608, β = 22.5792; expected value: 0.72
Utility of mild chronic hepatitis C state	β, α = 521.2375, β = 155.6943; expected value: 0.77
Utility of mild chronic hepatitis C state while on treatment (non-Peg IFN!)	β, α = 115.7063, β = 59.6063; expected value: 0.66
Utility of moderate chronic hepatitis C state	β, α = 168.2461, β = 86.6723; expected value: 0.66
Utility of compensated cirrhosis state	β, α = 47.1021, β = 38.5381; expected value: 0.55
Utility of decompensated cirrhosis state (and also HCC/liver transplant 1)	β, α = 123.7500, β = 151.2500; expected value: 0.45
Treatment effects	
IFN treatment effect for SVR – from Mild Hepatitis C trial	β, Integer parameters only, $n = 98$, $r = 32$; expected value: 0.33
SVR for IFN in moderate/severe disease	β, Integer parameters only, $n = 453$, $r = 198$; expected value: 0.44
SVR for PEG in mild disease	β, Integer parameters only, $n = 110$, $r = 55$; expected value: 0.50
SVR for PEG in moderate/severe disease	β, Integer parameters only, $n = 444$, $r = 247$; expected value: 0.56
Treatment duration, mean and SD, from Mild Hepatitis C trial	Normal, mean = 37.8, SD = $15.6\sqrt{98}$; expected value: 37.8

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

HTA Commissioning Board

Members

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

Diagnostic Technologies & Screening Panel

Members

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

Ms Norma Armston, Freelance Consumer Advocate, Bolton

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

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

Ms Dea Birkett, Service User Representative, London

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

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

Dr David Elliman, Consultant in Community Child Health, Islington PCT & Great Ormond Street Hospital, London

Professor Glyn Elwyn, Research Chair, Centre for Health Sciences Research, Cardiff University, Department of General Practice, Cardiff

Professor Paul Glasziou, Director, Centre for Evidence-Based Practice, University of Oxford

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

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

Mr Stephen Pilling, Director, Centre for Outcomes, Research & Effectiveness, Joint Director, National Collaborating Centre for Mental Health, University College London

Mrs Una Rennard, Service User Representative, Oxford

Dr Phil Shackley, Senior Lecturer in Health Economics, Academic Vascular Unit, University of Sheffield

Dr Margaret Somerville, Director of Public Health Learning, Peninsula Medical School, University of Plymouth

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

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

Professor Martin J Whittle, Clinical Co-director, National Co-ordinating Centre for Women's and Childhealth

Dr Dennis Wright, Consultant Biochemist & Clinical Director, The North West London Hospitals NHS Trust, Middlesex

Pharmaceuticals Panel

Members

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

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

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

Professor John Geddes, Professor of Epidemiological Psychiatry, University of Oxford

Mrs Barbara Greggains, Non-Executive Director, Greggains Management Ltd

Dr Bill Gutteridge, Medical Adviser, National Specialist Commissioning Advisory Group (NSCAG), London

Mrs Sharon Hart, Consultant Pharmaceutical Adviser, Reading

Dr Jonathan Karnon, Senior Research Fellow, Health Economics and Decision Science, University of Sheffield

Dr Yoon Loke, Senior Lecturer in Clinical Pharmacology, University of East Anglia

Ms Barbara Meredith, Lay Member, Epsom

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

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

Dr Martin Shelly, General Practitioner, Leeds

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

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

Therapeutic Procedures Panel

Members

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

Dr Mahmood Adil, Deputy Regional Director of Public Health, Department of Health, Manchester

Dr Aileen Clarke, Consultant in Public Health, Public Health Resource Unit, Oxford

Professor Matthew Cooke, Professor of Emergency Medicine, Warwick Emergency Care and Rehabilitation, University of Warwick

Mr Mark Emberton, Senior Lecturer in Oncological Urology, Institute of Urology, University College Hospital

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

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

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

Dr Peter Martin, Consultant Neurologist, Addenbrooke's Hospital, Cambridge

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

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

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

Dr Karen Roberts, Nurse Consultant, Queen Elizabeth Hospital, Gateshead

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

Professor Scott Weich, Professor of Psychiatry, Division of Health in the Community, University of Warwick

Disease Prevention Panel

Members

Chair,
Dr Edmund Jessop, Medical Adviser, National Specialist Commissioning Advisory Group (NSCAG), London

Mrs Sheila Clark, Chief Executive, St James's Hospital, Portsmouth

Mr Richard Copeland, Lead Pharmacist: Clinical Economy/Interface, Wansbeck General Hospital, Northumberland

Dr Elizabeth Fellow-Smith, Medical Director, West London Mental Health Trust, Middlesex

Mr Ian Flack, Director PPI Forum Support, Council of Ethnic Minority Voluntary Sector Organisations, Stratford

Dr John Jackson, General Practitioner, Newcastle upon Tyne

Mrs Veronica James, Chief Officer, Horsham District Age Concern, Horsham

Professor Mike Kelly, Director, Centre for Public Health Excellence, National Institute for Health and Clinical Excellence, London

Professor Yi Mien Koh, Director of Public Health and Medical Director, London NHS (North West London Strategic Health Authority), London

Ms Jeanett Martin, Director of Clinical Leadership & Quality, Lewisham PCT, London

Dr Chris McCall, General Practitioner, Dorset

Dr David Pencheon, Director, Eastern Region Public Health Observatory, Cambridge

Dr Ken Stein, Senior Clinical Lecturer in Public Health, Director, Peninsula Technology Assessment Group, University of Exeter, Exeter

Dr Carol Tannahill, Director, Glasgow Centre for Population Health, Glasgow

Professor Margaret Thorogood, Professor of Epidemiology, University of Warwick, Coventry

Dr Ewan Wilkinson, Consultant in Public Health, Royal Liverpool University Hospital, Liverpool

Expert Advisory Network

Members

Professor Douglas Altman, Professor of Statistics in Medicine, Centre for Statistics in Medicine, University of Oxford

Professor John Bond, Director, Centre for Health Services Research, University of Newcastle upon Tyne, School of Population & Health Sciences, Newcastle upon Tyne

Professor Andrew Bradbury, Professor of Vascular Surgery, Solihull Hospital, Birmingham

Mr Shaun Brogan, Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE, Chief Executive, Regulation and Improvement Authority, Belfast

Ms Tracy Bury, Project Manager, World Confederation for Physical Therapy, London

Professor Iain T Cameron, Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark, Medical Writer & Consultant Pharmacist, Rossendale

Professor Collette Clifford, Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham, Edgbaston, Birmingham

Professor Barry Cookson, Director, Laboratory of Healthcare Associated Infection, Health Protection Agency, London

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

Professor Howard Cuckle, Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Dr Katherine Darton, Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux, Professor of Paediatric Epidemiology, London

Dr Keith Dodd, Consultant Paediatrician, Derby

Mr John Dunning, Consultant Cardiothoracic Surgeon, Cardiothoracic Surgical Unit, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw, Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles, Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby, Professor of Community Rehabilitation, Institute of General Practice and Primary Care, University of Sheffield

Professor Gene Feder, Professor of Primary Care Research & Development, Centre for Health Sciences, Barts & The London Queen Mary's School of Medicine & Dentistry, London

Mr Leonard R Fenwick, Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Mrs Gillian Fletcher, Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn, Professor of Medicine, Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham

Dr Neville Goodman, Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Robert E Hawkins, CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor Allen Hutchinson, Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Professor Peter Jones, Professor of Psychiatry, University of Cambridge, Cambridge

Professor Stan Kaye, Cancer Research UK Professor of Medical Oncology, Section of Medicine, Royal Marsden Hospital & Institute of Cancer Research, Surrey

Dr Duncan Keeley, General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping, Research Degrees Programme Director & Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy, Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay, Professor of Psychiatry for the Elderly, University of Leicester, Leicester General Hospital

Professor Julian Little, Professor of Human Genome Epidemiology, Department of Epidemiology & Community Medicine, University of Ottawa

Professor Rajan Madhok, Consultant in Public Health, South Manchester Primary Care Trust, Manchester

Professor Alexander Markham, Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Professor Alistaire McGuire, Professor of Health Economics, London School of Economics

Dr Peter Moore, Freelance Science Writer, Ashtead

Dr Andrew Mortimore, Public Health Director, Southampton City Primary Care Trust, Southampton

Dr Sue Moss, Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Mrs Julietta Patnick, Director, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler, Professor of Liaison Psychiatry, Royal South Hants Hospital, Southampton

Professor Chris Price, Visiting Professor in Clinical Biochemistry, University of Oxford

Professor William Rosenberg, Professor of Hepatology and Consultant Physician, University of Southampton, Southampton

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Dr Susan Schonfield, Consultant in Public Health, Hillingdon PCT, Middlesex

Dr Eamonn Sheridan, Consultant in Clinical Genetics, Genetics Department, St James's University Hospital, Leeds

Professor Sarah Stewart-Brown, Professor of Public Health, University of Warwick, Division of Health in the Community Warwick Medical School, LWMS, Coventry

Professor Ala Szczepura, Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor, Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster, Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@hta.ac.uk
http://www.hta.ac.uk

ISSN 1366-5278