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D Hartwell, J Jones, L Baxter and J Shepherd

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Abstract

Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation

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Objective: To assess the clinical effectiveness and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C virus (HCV) in three specific patient subgroups affected by recent licence changes: those eligible for shortened treatment courses [i.e. those with low viral load (LVL) and who attained a rapid virological response (RVR) at 4 weeks of treatment], those eligible for re-treatment following previous non-response or relapse, and those co-infected with human immunodeficiency virus (HIV).
Data sources: Fourteen electronic bibliographic databases, including the Cochrane Library, MEDLINE and EMBASE, were searched up to October 2009. Key hepatitis C resources and symposia, bibliographies of related papers and manufacturer submissions to the National Institute for Health and Clinical Excellence were also searched and clinical experts were contacted.
Review methods: A systematic review and economic evaluation were carried out. Titles and abstracts were screened for eligibility by one reviewer. Inclusion criteria were defined a priori and applied independently by two reviewers to the full text of retrieved references. For the clinical effectiveness review, studies were included if they were randomised controlled trials (RCTs) of adults with chronic HCV, restricted to the patient groups described above. The intervention was standard peginterferon and ribavirin combination therapy compared with shortened duration courses (24 weeks for genotype 1, 16 weeks for genotype 2/3) or best supportive care (BSC). Outcomes included sustained virological response (SVR), relapse rate and adverse events. In addition, full economic evaluations and studies of health-related quality of life were sought for this subgroup of patients. Data extraction and quality assessment were undertaken by two reviewers independently. Studies were synthesised through a narrative review with tabulation of results. Our previously published Markov state-transition model was adapted to estimate the cost-effectiveness of treatment strategies in subgroups of adults with chronic HCV who were eligible for shortened treatment and re-treatment and those with HCV/HIV co-infection. The model extrapolated the impact of SVR on life expectancy, quality-adjusted life expectancy and lifetime costs for each subgroup of patients with HCV. Categories of costs included in the model were drug acquisition, patient management, on-treatment monitoring, management of adverse events, and health-state costs for disease progression.
Results: In total, 2400 references were identified. Six RCTs were included in the review of clinical effectiveness, all reporting peginterferon alfa and ribavirin therapy in patients eligible for shortened treatment. In general, these RCTs were of good quality. No RCTs

comparing peginterferon and ribavirin with BSC were identified for the re-treatment or co-infection populations. The results suggest that chronic HCV patients who have LVL at baseline and who achieve an RVR can be treated with shortened courses of therapy (24 weeks for genotype 1, 16 weeks for genotype 2/3) and achieve SVR rates that are comparable to those who receive the standard duration of treatment (ranges 84%–96% vs 83%–100%, respectively). However, patient numbers in the LVL/RVR subgroups were small and none of the trials was powered for this subgroup analysis, so results should be interpreted with caution. In the one trial reporting virological relapse rates in the subgroup of patients with LVL/RVR, rates were low and not statistically significantly different between those treated for 24 versus 48 weeks [3.6% vs 0%, respectively, difference 3.6%, 95% confidence interval (CI) –7.2% to 6.6%, $p = 1.000$]. In the cost-effectiveness analysis of shortened treatment with peginterferon alfa-2a, incremental cost-effectiveness ratios (ICERs) ranged from £35,000 to £65,000 for patients with genotype 1, whereas in patients with genotypes 2 and 3 shortened treatment dominated standard treatment. For patients with genotype 1 with LVL/RVR, shortened treatment with peginterferon alfa-2b dominated standard treatment. In patients with genotype 1 and those with genotype non-1 who were re-treated with peginterferon alfa-2a, the ICERs were £9169 and £2294, respectively. In patients with genotypes 1 and 4, who were re-treated with peginterferon alfa-2b, the ICER was £7681, whereas re-treatment dominated BSC for patients with genotypes 2 and 3. In patients co-infected with HCV/HIV, who were receiving peginterferon alfa-2a, the ICER was £7941 per quality-adjusted life-year (QALY) gained in patients with genotypes 1 and 4, whereas in patients with genotypes 2 and 3 peginterferon alfa-2a dominated BSC. In co-infected patients receiving peginterferon alfa-2b the ICER was £11,806 in genotypes 1 and 4, and £2161 in genotypes 2 and 3.

Conclusions: The clinical trial evidence indicates that patients may be successfully treated with a shorter course of peginterferon combination therapy without compromising the likelihood of achieving an SVR. The economic evaluation shows that treatment with peginterferon alfa in the specified subgroups of patients with LVL/RVR will yield QALY gains, without excessive increases in costs, and may be cost saving in some situations. However, a judgement is required on the value of the QALY loss that may result from adopting a shorter treatment regimen, if shorter treatment is associated with a lower SVR than standard treatment duration. There is a need for further RCT evidence, particularly in people who have not responded to, or relapsed following, treatment. Phase II and Phase III trials are currently in progress, evaluating the safety and efficacy of protease inhibitors and nucleoside analogues for treatment-naive and treatment-experienced people with chronic HCV.

Funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

List of abbreviations

ALT	alanine aminotransferase
BNF	*British National Formulary*
BSC	best supportive care
CC	compensated cirrhosis
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CrI	credible interval
CUA	cost–utility analysis
DC	decompensated cirrhosis
DSA	deterministic sensitivity analysis
EOT	end of treatment (virological response)
EQ-5D	European Quality of Life-5 Dimensions
EVR	early virological response
GGT	γ-glutamyltransferase
Gp	group
HAART	highly active antiretroviral therapy
HAI	histological activity index
Hb	haemoglobin
HCC	hepatocellular carcinoma
HCHS	hospital and community health services
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPA	Health Protection Agency
HRQoL	health-related quality of life
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IDU	injecting drug user
ITT	intention to treat
IU	international unit
LT	liver transplantation
LVL	low viral load
MS	manufacturer's submission
MSM	men who have sex with men
NA	not available
NICE	National Institute for Health and Clinical Excellence
NR	not reported
pa	per annum
PCR	polymerase chain reaction
Post LT	post liver transplantation
PSA	probabilistic sensitivity analysis
PSS	Personal and Social Services
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RNA	ribonucleic acid
RR	relative risk/risk ratio
RVR	rapid virological response

SE	standard error
SG	standard gamble
SHTAC	Southampton Health Technology Assessments Centre
SPC	summary of product characteristics
SVR	sustained virological response
TA	Technology Appraisal
TAR	technology assessment report
TMA	transcription-mediated amplification
TTO	time trade-off
ULN	upper limit of normal
YLS	years of life saved

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 in the notes at the end of the table.

Executive summary

Background

Chronic infection with the hepatitis C virus (HCV) is a significant public health problem in England and Wales. It is thought that around 0.5% of people aged 15–59 years are chronically infected, although prevalence estimates vary both geographically and in different population groups. Progressive liver disease, as a result of chronic HCV infection, usually develops slowly over 20–50 years and may lead to cirrhosis, hepatocellular carcinoma, liver failure and eventual death. Symptoms are typically mild and non-specific but nevertheless can cause a decrease in quality of life (QoL). Peginterferon alfa and ribavirin combination therapy is currently used in the UK for treatment of chronic HCV, having been recommended by the National Institute for Health and Clinical Excellence (NICE). Successful treatment is considered to be attainment of a sustained virological response (SVR), defined as undetectable serum HCV ribonucleic acid (RNA) 6 months after cessation of treatment. Since these recommendations, there have been extensions to the licences for both peginterferons to allow patients who have a low viral load (LVL) and achieve a rapid virological response (RVR) at 4 weeks' treatment to receive shortened treatment courses; patients who relapsed or did not respond to a previous course of peginterferon alfa combination therapy to undergo a second course; and patients with HCV/human immunodeficiency virus (HIV) co-infection to receive treatment. This review focuses specifically on these new indications.

Objectives

To assess the clinical effectiveness and cost-effectiveness of peginterferon alfa plus ribavirin for the treatment of chronic HCV in three specific patient subgroups: those eligible for shortened treatment courses, those eligible for re-treatment following previous non-response or relapse; and those who are co-infected with HIV.

Methods

Clinical effectiveness

A sensitive search strategy was designed and applied to 14 electronic bibliographic databases (including the Cochrane Library, MEDLINE and EMBASE) from the year 2000 to October 2009. Bibliographies of retrieved papers were screened, key hepatitis C resources and symposia were searched, and experts were also contacted to identify any additional published and unpublished references. Manufacturers' submissions to NICE were also searched.

Titles and abstracts were screened for eligibility by one reviewer. Inclusion criteria were defined a priori and applied independently by two reviewers to the full text of retrieved papers using a standard form. Studies were eligible for inclusion if the participants were adults with chronic HCV, restricted to the patient groups described above. The relevant intervention was peginterferon alfa and ribavirin combination therapy (or monotherapy for those who were unable to tolerate ribavirin) compared with shortened-duration courses of combination therapy (24 weeks for genotype 1, 16 weeks for genotypes 2 and 3) or best supportive care (BSC). The outcomes included measures of virological response during and after treatment, and adverse effects. Only randomised controlled trials (RCTs) were eligible for inclusion.

Data extraction and assessment of methodological quality was undertaken by one reviewer and checked by a second. Differences in opinion were resolved through discussion at each stage. The trials were reviewed in a narrative synthesis with tabulation of the results of all included studies. A meta-analysis was not undertaken owing to differences in the drug regimens, and because outcome data were based on relatively small subgroups of the randomised patients.

Cost-effectiveness

A systematic review of economic evaluations of peginterferon alfa in the specified patient groups was undertaken using standard methods for evidence synthesis. We adapted our previously published economic model of antiviral treatment for chronic HCV to estimate the cost-effectiveness of peginterferon alfa-2a and peginterferon alfa-2b in subgroups of adults who were eligible for a shortened duration of treatment with peginterferon alfa; had failed to respond to or had relapsed on previous treatment with peginterferon alfa; or were co-infected with HCV/HIV. The perspective of the cost-effectiveness analysis was that of the UK NHS and Personal Social Services. The short-term outcome of treatment was SVR. The model extrapolated the impact of SVR on life expectancy, quality-adjusted life expectancy and lifetime costs for each subgroup of patients with HCV. Published QoL weights estimated for a UK trial in patients with chronic HCV were used to derive the quality-adjusted life-years (QALYs) associated with each treatment strategy. Resource use associated with antiviral treatment was estimated from clinical guidelines and advice from clinical practitioners. Drug costs were taken from the *British National Formulary* (No. 58). To estimate costs associated with the management of chronic HCV, values from a UK trial in patients with chronic HCV were used. Costs and benefits were discounted at 3.5%. Uncertainty was explored through probabilistic and deterministic sensitivity analysis.

Results

Clinical effectiveness

A total of 2400 references were identified. Six RCTs (reported in eight publications) were included in the review of clinical effectiveness, all reporting peginterferon alfa and ribavirin combination therapy in patients who were eligible for shortened treatment duration. No RCTs comparing peginterferon alfa with or without ribavirin with BSC were identified for the re-treatment or co-infection populations. Shortened treatment in patients with genotype 1 was evaluated in four trials, genotype 2 in one trial, and genotypes 2 and 3 in one trial. In five of the trials, patients had LVL at baseline (based on mean viral load). Assessment of methodological reporting and quality varied between the included studies but was judged as good overall.

In the subgroup of patients who achieved an RVR and had LVL [< 400,000 international units (IU)/ml or ≤ 800,000 IU/ml] at baseline, SVR rates were comparable between groups who received standard treatment (range 83%–100%) and shortened treatment (range 84%–96%), with no statistically significant differences between groups. Rates were broadly similar regardless of genotype. However, none of the studies was statistically powered for these relatively small subgroups and results should therefore be interpreted with caution.

For both genotype 1 and genotype 2 and 3 patients, there were no statistically significant differences in rates of RVR between treatment groups that received the standard duration of treatment compared with those that received shortened courses. The proportion of patients achieving an RVR was observed to be higher in those with genotypes 2 and 3 than in those with genotype 1.

In the one trial reporting virological relapse rates in the subgroup of patients with an RVR and LVL, rates were low and not significantly different between those treated for 24 versus 48 weeks

(3.6% vs 0% respectively, $p = 1.000$). Adverse events were reported for treatment groups as a whole and the reporting of statistical tests varied. The most frequently occurring adverse events were similar across all of the trials and included flu-like symptoms, insomnia, anorexia, dermatological symptoms and alopecia. There was a trend for a lower incidence of adverse events and fewer dose discontinuations in patients receiving a shortened treatment regimen, although on the whole there were no statistically significant differences between treatment arms (where reported). None of the trials measured QoL as an outcome measure.

Cost-effectiveness

The systematic review of cost-effectiveness studies identified two published economic evaluations that met the inclusion criteria, both of which focused on patients co-infected with HCV/HIV. The included economic evaluations used Markov models to extrapolate from SVRs reported in clinical trials to life expectancy and (in one case) quality-adjusted life expectancy gains associated with antiviral treatment strategies for patients who were co-infected with HCV/HIV. Both evaluations indicated that HCV antiviral treatment was associated with gains in life expectancy for HCV/HIV co-infected patients. A systematic search for published studies of QoL found no relevant studies.

Roche submitted a dossier in support of peginterferon alfa-2a combined with ribavirin in three subgroups of patients: shortened duration of treatment for patients with LVL who exhibited an RVR; re-treatment in patients who did not respond or relapsed on previous treatment with peginterferon alfa; and treatment of patients with HCV/HIV co-infection. Roche's base-case results comparing shortened treatment with standard treatment duration indicated positive ICERs of £15,472 per QALY gained for genotype 1 and 4 patients and £2719 for genotypes 2 and 3 with LVL and RVR. For non-responders, comparing re-treatment with BSC, the ICERs were £3334 and £809 per QALY gained for genotypes 1 and 4, and 2 and 3, respectively. Re-treatment with peginterferon alfa dominated BSC in patients who relapsed after previous treatment. Roche reported that, overall in patients co-infected with HCV/HIV, peginterferon dominated non-peginterferon and ribavirin combination therapy.

Schering-Plough submitted a dossier in support of peginterferon alfa-2b combined with ribavirin in two of the three subgroups of patients within the scope of the NICE appraisal: re-treatment in patients who did not respond or relapsed on previous treatment with peginterferon alfa, and treatment of patients with HCV/HIV co-infection. For re-treatment with peginterferon alfa-2b compared with BSC, the overall ICER in non-responders/relapsers was £4387 per QALY gained. In genotypes 1 and 4 the ICER was £7177, and in genotypes 2 and 3 it was £783 per QALY gained. The ICER for peginterferon alfa-2b in HCV/HIV patients compared with BSC was £1637 in genotypes 1 and 4, and £403 in patients with genotypes 2 and 3. The ICER for all patients was £1077.

In our base-case analysis, SVRs for peginterferon alfa-2a from two trials included in our systematic review of clinical effectiveness were used to model cost-effectiveness in genotype 1 patients who were eligible for shortened treatment. The ICERs ranged from £35,000 to £65,000. A further two trials from our systematic review were used to model cost-effectiveness in genotype 2 and 3 patients in this group. In this case, shortened treatment dominated standard treatment duration. For genotype 1 patients with LVL and RVR, shortened treatment duration with peginterferon alfa-2b dominated standard treatment.

In genotype 1 and genotype non-1 patients who were re-treated with peginterferon alfa-2a, the ICERs were £9169 and £2294, respectively. In genotype 1 and 4 patients who were re-treated with peginterferon alfa-2b, the ICER was £7681, whereas re-treatment dominated BSC for genotype 2 and 3 patients. In HCV/HIV co-infected patients receiving peginterferon alfa-2a the ICER was

£7941 per QALY gained in genotype 1 and 4 patients, whereas peginterferon alfa-2a dominated BSC in genotypes 2 and 3. In co-infected patients receiving peginterferon alfa-2b the ICER was £11,806 in genotypes 1 and 4, and £2161 in genotypes 2 and 3.

Discussion

The evidence suggests that patients can receive shorter courses of peginterferon combination therapy without compromising the likelihood of achieving an SVR. However, SVRs according to baseline LVL and RVR were based on subgroups of varying sizes of the randomised patients, and these are likely to be underpowered. The results of the trials in these subgroups should therefore be regarded as speculative.

There is substantial uncertainty over the data used to populate the economic model, with little evidence available to update the model for the subgroups of patients covered by the review.

Conclusions

In summary, the clinical trial evidence indicates that patients may be successfully treated with a shorter course of peginterferon alfa and ribavirin combination therapy for 16 weeks (genotypes 2 and 3), or 24 weeks (genotype 1), without compromising SVR rates. However, the cost-effectiveness analyses indicate that a judgement is required on the value of the QALY loss that may result from adopting shorter treatment duration, if shorter treatment duration is associated with a lower SVR than standard duration. The cost-effectiveness results submitted by the manufacturers and those reported in our independent analysis suggest that treatment with peginterferon alfa in the specified subgroups of patients will yield QALY gains, without excessive increase in costs, and may be cost saving in some situations.

There is a need for further RCT evidence, particularly in people who have not responded to, or who have relapsed following, treatment. Phase II and Phase III trials are currently in progress, evaluating the safety and efficacy of protease inhibitors and nucleoside analogues for treatment-naive and treatment-experienced people with chronic HCV infection.

Funding

The National Institute for Health Research Health Technology Assessment programme.

Chapter 1

Background

Description of underlying health problem

Hepatitis C is a slowly progressing infectious disease of the liver arising from the blood-borne hepatitis C virus (HCV). First identified in 1989, HCV belongs to the Flaviviridae family of viruses. It is a ribonucleic acid (RNA) virus, of which there are six genetic variations, known as genotypes (e.g. 1, 2, 3, etc.), the prevalence of which varies considerably between countries.[1,2] In England and Wales, the most prevalent genotypes are 1 and 3, representing more than 90% of all diagnosed infections.[3] Genotype 3a remains the most common, with a prevalence of 39%, followed by genotype 1a (22%).[3] Response to treatment is strongly influenced by HCV genotype (see *Current service provision* and *Description of technology under assessment*).

There are two main phases of infection: acute and chronic. Acute HCV refers to the period immediately after HCV infection, whereas chronic HCV (the focus of this report) is defined as infection persisting for > 6 months. Of those exposed to HCV, approximately 20% will clear the virus spontaneously, although the remaining 80% will go on to develop chronic infection. Chronic HCV is categorised as mild, moderate or severe according to the extent of liver damage, based on both the level of fibrosis (scarring) that has occurred in the liver as well as the degree of necroinflammation (inflammation and destruction of liver tissue) (see *Disease progression and prognosis*). Symptoms in people with chronic HCV are typically mild and non-specific, and include fatigue, flu-like symptoms, anorexia, depression, sleep disturbance, cognitive impairment, right upper quadrant pain, itching and nausea.[4,5] Although the symptoms are mild in some people, in others they can cause a significant decrease in quality of life (QoL) irrespective of the degree of liver damage.[6] Symptoms and signs of chronic HCV-related liver damage may occur later in the disease when scarring of the liver has progressed.

Aetiology

Hepatitis C virus is transmitted parenterally (i.e. via routes other than the digestive tract) and is acquired primarily through exposure to contaminated blood. The most common source of HCV transmission in the UK is through the sharing of injecting paraphernalia during illicit intravenous drug use, accounting for around 90% of cases.[3] Other less common sources of infection include mother–baby transmission, occupational exposure (e.g. via needlestick injury), tattooing and body piercing. Before the introduction of blood screening in 1991, it was also spread through the use of contaminated blood products or organ transplantation. In some resource-poor countries it is thought that infections may occur through the use of unsterilised needles in health-care settings. The risk of sexual transmission has been thought, traditionally, to be low. For example, the Health Protection Agency (HPA) estimates that only 1.4% of infections identified through laboratory reports between 1996 and 2007 were attributed to sexual exposure.[3] However, increasing numbers of acute infections in human immunodeficiency virus (HIV)-positive men who have sex with men (MSM) suggests potential for transmission associated with high-risk sexual practices probably involving blood (see below).[7]

Epidemiology

Prevalence

The estimated global prevalence of chronic HCV is around 2%–3%, corresponding to about 130–170 million people.[1,8] In England and Wales, the HPA[3] estimates that, based on statistical

model data for the year 2003, around 191,000 [95% credible interval (CrI) 124.00 to 311.00] people aged 15–59 years are HCV antibody positive, with 142,000 people chronically infected, a prevalence of 0.44% (95% CrI 0.29% to 0.72%) in this age group.

Prevalence estimates vary geographically in England and Wales, with highest numbers of laboratory reports (from public health and UK NHS laboratories in England and Wales under a voluntary surveillance scheme) returned in the north-west, followed by London and the south-east of England.[3]

The prevalence of chronic HCV also varies according to different population groups. For example, HCV is more common in men and in the 25–44 years age group. Estimates of the number of current injecting drug users (IDUs) in England vary between 100,000 and 217,000, and it is estimated that around 40% of IDUs are infected with chronic HCV, based on the Unlinked Anonymous Prevalence Monitoring Programme's Survey of Injecting Drug Users in 2006.[9] There are limited data on prevalence in minority ethnic populations. However, it is thought that the prevalence of HCV is higher in migrants who will have acquired the infection while overseas, notably Pakistan.[3]

Evidence suggests varying rates of HCV in people with HIV infection. For example, Mohsen and colleagues[10] reviewed the international literature on the epidemiology of HCV/HIV co-infected patients. They included 12 HCV seroprevalence studies carried out in people infected with HIV-1 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%). It has been suggested that up to 10% of all HCV-infected people are co-infected with HIV.[11]

Prevalence is difficult to estimate because symptoms of HCV are frequently absent or non-specific and thus people can remain undiagnosed for many years. Between 1992 and 2007 there were 62,000 laboratory-confirmed diagnoses of HCV in England, and 3688 in Wales (from 1996).[3] It is thought that a proportion of those who are undiagnosed are ex-IDUs who used drugs transiently in the past. Sentinel surveillance by the HPA suggests that the number of people diagnosed with HCV in all settings is increasing, which may, in part, reflect awareness-raising campaigns to encourage uptake of testing.[3]

Incidence

The incidence of chronic HCV is likely to be driven by two main sources – newly acquired infections in current UK residents (largely IDUs) and inward migration of chronically infected individuals from other countries. Up-to-date estimates of overall incidence are not yet available but recent studies in IDUs suggest that 3%–42% of susceptible injectors become infected each year.[3] The HPA reports that the number of laboratory-confirmed diagnoses of HCV in England and Wales in 2007 was 7540, representing a 12% increase from 2006.[3] This does not, however, necessarily represent an increase in rates of incidence but may be attributed to testing rates.

Recent rises in HCV infection in HIV-positive MSM have generated increased interest in the role of sexual transmission of HCV. HCV RNA can be detected in the semen of HCV-infected men, with higher levels in HIV-positive men, suggesting the possibility of transmission during certain sexual practices. Increases in cases of acute co-infection in HIV-positive MSM in urban centres in Europe and the USA have been reported in recent years.[12] A study of genitourinary medicine (GUM) clinics in London and the south-east of England found a 20% average annual increase in the number of HIV-positive MSM diagnosed with HCV between January 2002 and June 2006.[7] The prevalence of HCV in HIV-positive MSM is estimated to be between 4% and 11.5%.[12]

Disease progression and prognosis

Chronic HCV infection is associated with progression to liver failure in some, but not all, people. Progressive liver disease is characterised by inflammation of the liver, which leads to gradual fibrosis, which, in its severe form, produces cirrhosis. Cirrhosis can progress from a compensated state (where the liver is still functioning despite the fibrosis) to a decompensated state (where the functioning of the liver is seriously impaired). Decompensation is characterised by complications such as ascites (large accumulations of fluid in the abdominal cavity), variceal bleeding (enlarged and bleeding veins around the oesophagus) and hepatic encephalopathy (neuropsychiatric abnormalities, such as cognitive impairment associated with liver dysfunction). There are a number of commonly used systems for classifying the severity of HCV-related liver disease from biopsy samples. Some share common characteristics and are derived from the same systems.[13] Three commonly cited systems are the Knodell histological activity index (HAI),[14] the Ishak revised HAI[15] and the METAVIR system.[16] The Ishak system,[15] for example, classifies mild HCV as a fibrosis score of ≤ 2 and a necro-inflammation score of between 1 and 8, moderate HCV as a fibrosis score of 3–5 and a necro-inflammation score of 0–18 (moderate/severe), and severe HCV as a fibrosis score of 6 (cirrhosis). If the fibrosis score reaches '6' the patient is classified as having severe HCV-related liver damage, irrespective of the necro-inflammation score (see our previous technology assessment report[17] on antiviral treatment for mild HCV for further detail on liver biopsy classification systems).

Cirrhosis can develop rapidly, within 1–2 years of exposure (although this is rare), but more usually develops slowly over two to three decades. A recent Markov modelling study[18] of three different observational cohorts in the UK estimated that between 6% and 23% of people will progress to cirrhosis after 20 years of infection. The estimates were highly sensitive to the type of cohort used, with lower estimates from the HCV National Register lookback cohort, comprising individuals identified from blood screening and donor surveillance schemes, and highest estimates from a London-based tertiary referral centre in which patients underwent a biopsy. Estimates of progression to cirrhosis from retrospective studies are higher, with between 17% and 55% of patients progressing between 10 and 30 years following infection.[19] It is estimated that 6%–10% of cirrhotic patients will progress to decompensated cirrhosis.[19]

A recent modelling study estimated that in England the number of HCV-infected people living with compensated cirrhosis will rise from 3705 (95% CrI 2820 to 4975) in 2005 to 7550 (95% CrI 5120 to 116,400) in 2015.[20]

Patients with HCV-related cirrhosis are at risk of developing hepatocellular carcinoma (HCC) with an annual incidence of 1%–4%.[21] Some patients with decompensated cirrhosis or HCC may require liver transplantation. In 2007, 482 liver transplants were conducted in England, of which 13% ($n = 64$) were classified as first liver transplants with post-HCV cirrhosis at registration/HCV positive at registration or transplant.[3] However, demand for liver donors remains high and not all patients will be considered for transplantation. The number of people with decompensated cirrhosis and/or HCC is also estimated to rise from 1150 (95% CrI 1055 to 1250) in 2005 to 2540 (95% CrI 2035 to 3310) in 2015.[20]

Risk factors associated with rapid disease progression include male gender, excessive alcohol consumption and age at infection.[19] For example, Poynard and colleagues[22] studied a cohort of 2313 untreated patients and reported that increasing age at infection was independently associated with disease progression. Two per cent of those infected before the age of 20 years developed cirrhosis over a 20-year period compared with 6% of those infected between the ages of 31 and 40 years, 37% infected between 41 and 50 years, and 63% infected after the age of 50 years. HCV genotypes and HCV RNA viral load, although important in governing the

effectiveness of treatment regimens (see *Shortening the course of treatment*), are not thought to influence the natural course of infection.[19]

Co-infection with HIV is also associated with rapid HCV-related disease progression.[23–25] Since the introduction of highly active antiretroviral therapy (HAART) in the mid to late 1990s, patients with HIV infection are living longer and therefore those who are co-infected are becoming at risk of long-term chronic HCV-related liver disease. Mohsen and colleagues[26] reported a study of 153 HCV-infected and 55 HCV/HIV co-infected patients (72% of whom were receiving antiretroviral therapy at time of liver biopsy) from two London hospitals. The estimated median fibrosis progression rate was 0.17 units/year in HCV/HIV co-infected patients and 0.13 in HCV mono-infected patients ($p = 0.01$). This equates to estimated times from HCV infection to cirrhosis of 23 and 32 years, respectively. HIV positivity and a low CD4 cell count were among a number of factors that were independently related to fibrosis progression. A retrospective analysis by Poynard and colleagues[27] of 4852 patients with chronic liver disease of a variety of causes found that HCV/HIV co-infection was associated with the fastest fibrosis progression compared with causes such as genetic haemochromatosis, primary biliary cirrhosis and alcoholic liver disease. Despite the findings of these studies it has been suggested that the effective immune restoration observed with HAART can, indirectly, reduce the rate of liver fibrosis to a value that is comparable with the rate of HCV mono-infected people,[12] although a systematic review of natural history studies in co-infected patients concluded that this was not necessarily the case.[28]

Given the slowing of HIV-related disease progression and extended survival associated with HAART[29] it could be assumed that HCV is now one of the major causes of mortality in people with HIV.[11] However, although there has been an increase in liver disease-related deaths in co-infected patients, it is not clear whether this is associated with HAART-related toxicity or HCV-related liver disease, as studies have shown mixed findings.[30,31]

Diagnosis

Presence of HCV infection may be detected through the identification of antibodies using enzyme-linked immunosorbent assays (ELISAs) and then confirmed through the identification of HCV RNA in serum.[32] The latter can be carried out using sensitive molecular assays, such as polymerase chain reaction (PCR). A detectable HCV viral load of 50 international units (IU)/ml or above is generally considered indicative of infection, although newer assays have a lower threshold of detectability of 12–20 IU/ml. As part of the diagnostic process, patients receive testing to determine their genotype, as this is associated with the efficacy of treatment and will govern the duration of therapy (see *Shortening the course of treatment*). Alanine aminotransferase (ALT) biochemical tests are also used to indicate potential HCV-related liver damage, but are not necessarily used to determine eligibility for treatment.

Traditionally, a liver biopsy has been used to gauge the extent of HCV-related liver damage in order to guide treatment decisions. If the biopsy sample showed significant fibrosis or cirrhosis, clinicians would probably commence antiviral treatment. However, there has been a shift away from using biopsy in recent years for a number of reasons, including the risk of complications (e.g. a small risk of hepatic bleeding), the pain and discomfort to the patient, the lack of interobserver reliability between pathologists, and the suggestion that it may discourage some patients from presenting for assessment. Furthermore, guidance from organisations such as the National Institute for Health and Clinical Excellence (NICE)[33] to extend the provision of treatment to those with mild HCV means that it is no longer necessary to use biopsy to gauge disease severity in order to determine when to begin treatment.

Nevertheless, some clinicians find liver biopsy a useful tool to detect the presence or absence of steatosis (fatty liver) and other potential confounding liver diseases. This is reflected by NICE's

guidance, which states that clinicians may conduct a biopsy, if required, for other reasons,[33] and also by Scottish guidelines on the management of HCV, which state that liver biopsy should be considered if there is concern about additional causes of liver disease.[32] Patients may also seek a biopsy to determine the extent of any fibrosis to help them decide whether or not to commence treatment.

The development of non-invasive serum markers and other technologies (e.g. ultrasound) as an alternative to biopsy has generated interest in recent years, although their clinical effectiveness and cost-effectiveness have not yet been appraised at policy level in England and Wales.

Current service provision

Antiviral treatment

The majority of people with chronic HCV will not clear the virus spontaneously and will need to be assessed for possible antiviral treatment. Patients with chronic HCV are generally managed in specialist hepatology centres. They may also be managed by gastroenterologists and specialists in infectious diseases. Specialist hepatology nurses are also involved, particularly in the administration of antiviral treatment.

The primary aim of treatment is to clear the virus from the blood, and success is usually taken to be a sustained virological response (SVR), defined as a drop in serum HCV RNA to undetectable levels (e.g. below 50 IU/ml) 6 months after the end of treatment. An SVR is generally considered to indicate permanent resolution of infection, although relapse may occur in around 5% of cases after 5 years.[34] Studies (mostly observational) have reported that people who achieve an SVR have a lower probability of developing HCC[35] and liver-related death[36] than those that do not. However, the validity of SVR as a surrogate for long-term clinical outcomes – such as decompensated liver disease, HCC and death – has been questioned.[37] It is suggested that this is because of an absence of randomised controlled trials (RCTs) in which the effects of antiviral treatment, in terms of SVR, have been correlated with long-term clinical outcomes. The exception is for cirrhotic patients in whom some evidence of a correlation between SVR and HCC has been identified (based on studies of treatment with interferon alfa monotherapy).[37] It is recommended that several RCTs of antiviral treatment, with long-term follow-up over a number of years, are required to determine the validity of a surrogate outcome.[37] Given that this is unlikely to be practical, and the general acceptance of SVR as being the most reliable measure of HCV infection resolution, it is pragmatic to assume that an SVR, in most people, will reduce the likelihood of morbidity and mortality.

Interferon alfa, originally as monotherapy and then as combination therapy with ribavirin, was the mainstay of treatment until the pegylated forms of interferon (peginterferon alfa or α) were introduced in 2002. The peginterferons are cytokines, the mechanism of which is to assist the immune response by inhibiting viral replication. Two forms are available: peginterferon alfa-2a (Pegasys®, Roche Products) and peginterferon alfa-2b (ViraferonPeg®, Schering-Plough). Ribavirin is a synthetic nucleoside analogue that is available in three forms: Copegus® (Roche Products), Rebetol® (Schering-Plough) and Ribavirin Teva (Teva UK). Copegus is licensed only for combination therapy with peginterferon alfa-2a, whereas Rebetol and Ribavirin Teva are licensed only for combination therapy with peginterferon alfa-2b.

The current NICE guidance [Technology Appraisal (TA) 106,[33] an extension of TA 75[38]] recommends combination therapy with ribavirin and either peginterferon alfa-2a or peginterferon alfa-2b for adult patients with chronic HCV, regardless of disease severity. Monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is recommended for patients

who are unable to tolerate ribavirin or for whom ribavirin is contraindicated. For those with mild HCV, the decision whether to treat immediately or adopt an approach of 'watchful waiting' is made by the patient and clinician on an individual basis. The standard duration of treatment is 24 or 48 weeks, depending on a combination of factors including the genotype, initial viral load, and rapid and early virological response (EVR) to treatment. Treatment is currently restricted to patients who:

- are treatment naive
- have previously been treated with non-peginterferon alfa combination therapy or monotherapy
- have previously been treated with peginterferon alfa monotherapy but did not respond or subsequently relapsed.

It is not thought that there are substantial variations in practice across the country in terms of antiviral treatment, although clinical management of chronic HCV may vary according to the availability of hepatologists and specialist clinics.

There are a number of specific areas in which the clinical management of HCV infection is evolving, including prescribing shorter treatment courses, re-treating patients who have not responded or relapsed to a previous course, and treating patients who are co-infected with HCV/HIV. These areas are discussed in the following subsections.

Shortening the course of treatment

In recent years, one of the key aims of the management of HCV has been to maximise the likelihood of an SVR while minimising potential adverse effects of treatment. The adverse effects associated with interferon-based antiviral treatment (e.g. flu-like symptoms, nausea, vomiting, depression) and ribavirin (e.g. anaemia) can be significant, and some patients describe it as a very unpleasant experience, disrupting their social and family life, and, in some cases, impairing their ability to work. Sparing them the potential adverse effects through shorter but effective treatment courses will make therapy more tolerable, and may have the additional advantage of encouraging more people with suspected HCV to present for diagnosis, assessment and treatment.

To demonstrate the efficacy of shortened courses of treatment, clinical trials have measured viral response at interim time points after commencement of therapy to determine the likelihood of an SVR. An EVR is measured after 12 weeks of therapy and is generally defined as either a negative HCV RNA (complete EVR) or a minimum two $\log_{10}$ drop in quantitative HCV RNA levels (partial EVR).[39] EVR tends to be measured in genotype 1 patients to determine whether to stop treatment at 12 weeks in non-responders (patients who do not achieve an EVR generally do not go on to achieve an SVR with continued treatment) or to continue for 48 weeks in those who have responded.

Recently, there has been a focus on identifying responders earlier than 12 weeks. A rapid virological response (RVR) is measured at week 4 of therapy and is generally defined as a negative qualitative HCV RNA. Thresholds for negativity vary according to the assay, with some assays using a lower limit of detectability of 50 IU/ml, and others using thresholds as low as 12 IU/ml. RVR tends to be measured in genotype 2 or 3 patients in order to determine whether treatment can be shortened from 24 to 16 weeks, and in genotype 1 or 4 patients to determine whether treatment can be shortened from 48 to 24 weeks.

Decisions regarding the most appropriate length of treatment may also take into account baseline viral load in addition to genotype. Low viral loads (LVLs) have generally been associated with increased likelihood of an SVR in some clinical trials.[40,41] There does not appear to be a

consensus regarding what constitutes a low or high viral load. However, the manufacturers of peginterferon alfa-2a and peginterferon alfa-2b consider LVL as being HCV RNA ≤ 800,000 and < 600,000 IU/ml, respectively.[42,43]

Re-treatment of non-responders and relapsers

Given the fact that, on average, SVRs are achieved by between only 50% and 60% of patients receiving antiviral therapy[17,44] (with variations according to factors such as genotype, baseline viral load and treatment regimen), it is important to establish the efficacy of re-treatment with a subsequent course for those who did not respond or who relapsed. A non-responder is a patient who has detectable HCV RNA throughout a course of antiviral treatment. A relapser is defined as a patient who achieves loss of detectable HCV RNA during treatment, but in whom HCV RNA reappears either while still on therapy or once therapy is stopped.

Current NICE guidance recommends the re-treatment of patients who have failed previous treatment with non-peginterferon alfa and ribavirin combination therapy or non-peginterferon alfa monotherapy, or peginterferon alfa monotherapy, providing they achieve an EVR (as defined above in *Shortening the course of treatment*).[33] However, the guidance does not currently make provision for patients who have not responded to, or failed, a previous course of, peginterferon alfa and ribavirin combination therapy.

If re-treatment with peginterferon alfa (with or without ribavirin, depending on contraindication) does not achieve an SVR, then it is unlikely that maintenance treatment to reduce progressive liver damage will be considered. At the present time there are no other licensed drugs that could be used as second-line treatment in patients with HCV.

Treatment of HCV/HIV co-infected patients

Effective clinical management of people co-infected with HCV and HIV is important, given the increased rate of HCV-related disease progression in this group (as discussed in *Disease progression and prognosis*). For example, treatment decisions need to take into account any possible drug interactions between HCV antiviral medication and HAART [e.g. didanosine (Videx®, Bristol–Myers Squibb), which is contraindicated in co-infected patients taking antiviral treatment for HCV].[45] There is potential for significant HAART-associated hepatotoxicity in co-infected patients, which in serious cases may necessitate the withdrawal of HAART, with subsequent potential for the development of resistance to HIV medication.[11] The adverse effects of HCV antiviral medication may be more pronounced in co-infected patients, notably depression.

Given the complexity of managing both infections, clinical guidelines on the management of HCV/HIV co-infected people recommend that treatment be led by specialists in both HIV and HCV.[46] Treatment with peginterferon alfa and ribavirin in combination is recommended unless contraindicated.[45,46] Although HCV/HIV co-infected people were not the focus of NICE's previous technology appraisals, the guidance does recommend antiviral treatment for this group, in common with that for HCV mono-infected people.[33,38]

Description of technology under assessment

The intervention under assessment in this report is peginterferon alfa-2a and alfa-2b in combination with ribavirin (or as monotherapy if ribavirin is contraindicated). Peginterferon alfa-2a was licensed in June 2002, with extensions to the licence granted in June 2007. The recommended dose is 180 µg once per week, administered subcutaneously, for 16, 24 or 48 weeks, dependent on genotype, baseline viral load and treatment response. Peginterferon

alfa-2b was licensed in February 2002, with extensions to the licence granted in May 2005. The recommended dose is 1.5 µg/kg body weight once per week, administered subcutaneously for 24 or 48 weeks, dependent on genotype, baseline viral load and treatment response.

The three forms of ribavirin (Rebetol, Copegus and Ribavirin Teva) were licensed in May 1999, November 2002 and March 2009, respectively. The recommended dose of ribavirin ranges from 800 mg to 1400 mg taken orally each day in two divided doses (200-mg capsules), with the dose depending on the patient's body weight. The dose of Copegus also varies according to genotype [800 mg per day for genotype 2/3 and 1000–1200 mg per day (depending on body weight: 1000 mg for weight < 75 kg, 1200 mg for weight ≥ 75 kg) for genotype 1].

For both forms of peginterferon alfa, the therapeutic indication is the treatment of adult patients with chronic HCV who are positive for serum HCV RNA, including those with clinically stable HIV co-infection. The preferred indication is in combination with ribavirin, but monotherapy is indicated in cases of intolerance or contraindication to ribavirin. Patients may be treatment naive or may have failed previous monotherapy or combination treatment.

For peginterferon alfa-2a, genotype 1 patients with detectable HCV RNA at 4 weeks (i.e. no RVR) should receive 48 weeks' treatment. Those with genotype 2/3 and detectable HCV RNA at 4 weeks should receive 24 weeks' treatment. The licence extensions allow genotype 1 patients with LVL, an RVR and undetectable HCV RNA at week 24 to complete treatment at week 24 rather than receive the standard 48 weeks' treatment. It also allows genotype 2/3 patients with LVL (≤ 800,000 IU/ml), an RVR and undetectable HCV RNA at week 16 to finish treatment at week 16 rather than receive the standard 24 weeks' treatment. Those with genotype 4 may be treated as genotype 1, without the requirement for LVL. It is recommended that patients receiving peginterferon monotherapy be treated for 48 weeks.

For peginterferon alfa-2b, genotype 1 patients with an EVR (at week 12) should receive 48 weeks' treatment. Those without an EVR are considered unlikely to achieve an SVR and consideration should be given to withdrawal of treatment. Genotype 2/3 patients should be treated for 24 weeks. Licence extensions permit genotype 1 patients with LVL (< 600,000 IU/ml) and an RVR and undetectable HCV RNA at week 24 to receive 24 weeks' treatment rather than 48. The licence does not permit, however, shorter courses of treatment in genotype 2, 3 or 4 patients. Patients receiving peginterferon monotherapy who achieve an EVR should continue treatment for another 3 months. Extension of treatment to 1 year should be based on prognostic factors such as age and genotype.

For both peginterferon alfa-2a and alfa-2b, patients co-infected with HIV should be treated for 48 weeks, regardless of genotype. Full details of the indications, dosages and duration of treatment are given in the summaries of product characteristics (SPCs).[42,43]

In terms of costs, a 180-µg prefilled syringe of peginterferon alfa-2a (the recommended weekly dose) costs £126.91. A 168 × 200 mg-tab pack of ribavirin (Copegus) costs £444.43. The weekly cost of Copegus would be £111 for genotype 1 (based on 1200 mg per day for an average body weight of 79 kg) and £74 for genotype 2/3 (based on 800 mg per day for an average body weight of 79 kg). A 120-µg prefilled injection pen of peginterferon alfa-2b costs £162.60. This would be the weekly cost for an average patient weighing 79 kg (1.5 µg per kg). A 168 × 200 mg-tab pack of ribavirin (Rebetol) costs £327. The weekly cost of for Rebetol would be £68, based on 1000 mg per day for an average body weight of 79 kg. All costs are from the *British National Formulary* (*BNF*), No. 58, September 2009.[47] [See *Chapter 5* (*Cost data*) for full details of the drug costs estimated in our independent economic evaluation.]

Chapter 2

Definition of the decision problem

Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of moderate to severe HCV was appraised by NICE in 2004 (TA75),[38] and an appraisal specifically for mild HCV was carried out in 2006 (TA106).[33] Both appraisals were based on our independent assessment reports.[17,44] Since NICE's clinical guidance was published, there have been extensions to the licences for peginterferon alfa-2a and alfa-2b. This health technology assessment (HTA) is a part-review of the current NICE guidance and is restricted to the patient subgroups that are affected by the licence extensions, as below.

Decision problem

The decision problem is based on the scope of the appraisal as set by NICE. The relevant intervention is peginterferon alfa (2a and 2b) in combination with ribavirin, or peginterferon alfa monotherapy where ribavirin is contraindicated. The population of interest is adult patients with chronic HCV infection in one or more of the following patient groups – those who (1) meet the licensed criteria for receiving shortened courses of combination therapy; (2) have been previously treated with peginterferon alfa and ribavirin in combination and who either did not respond or who responded but relapsed; and (3) are co-infected with HIV.

The relevant comparator for studies evaluating the efficacy of shortened treatment courses is standard treatment duration (e.g. 48 weeks for genotype 1 patients, 24 weeks for genotype 2/3 patients). For the other two patient groups the comparator is best supportive care (BSC). Relevant outcomes include virological response (e.g. during treatment, 6 months post treatment), biochemical response (e.g. ALT levels), histological improvement (fibrosis and inflammation), survival, adverse effects of treatment, and health-related quality of life (HRQoL).

Overall aims and objectives of assessment

The aim of this HTA is to assess the clinical effectiveness and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of chronic HCV in three specific patient groups: those eligible for shortened treatment courses; those eligible for re-treatment following previous non-response or relapse; and those who are co-infected with HIV.

Chapter 3

Methods

The a priori methods for systematically reviewing the evidence of clinical effectiveness and cost-effectiveness were described in a research protocol (see *Appendix 1*), which was sent to experts for comment. Minor amendments were made as appropriate but no comments that identified specific problems with the methods of the review were received. The methods of the Southampton Health Technology Assessments Centre (SHTAC) economic evaluation can be seen in *Chapter 5* (*Methods for SHTAC independent economic analysis*).

Identification of studies

A sensitive search strategy was developed and refined by an experienced information scientist and was based upon that used in previous technology assessment reports.[17,44] Separate searches were conducted to identify studies of clinical effectiveness, cost-effectiveness, QoL, resource use/costs and epidemiology. The different search strategies are provided in *Appendix 2*.

Searches for clinical effectiveness and cost-effectiveness literature were undertaken from April 2007 (the date the most recent search was conducted[48]) to October 2009. References identified in the previous hepatitis C technology assessment reports[17,44] in which literature searching extended back to the year 2000 were incorporated into the searches. Search filters were run, where possible, to locate RCTs and searches were restricted to the English language. The strategies were applied to the following databases:

- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Centre for Reviews and Dissemination (CRD) (University of York) databases: Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and the HTA database
- MEDLINE (Ovid)
- EMBASE (Ovid)
- PREMEDLINE In-Process & Other Non-Indexed Citations (Ovid)
- Web of Science with Conference Proceedings: Science Citation Index Expanded (SCIE) and Conference Proceedings Citation Index – Science (CPCI) (ISI Web of Knowledge)
- Biosis Previews (ISI Web of Knowledge)
- National Institute for Health Research (NIHR) Clinical Research Network Portfolio
- ClinicalTrials.gov
- Current Controlled Trials.

Bibliographies of retrieved papers were screened for relevant studies, and the manufacturers' submissions (MSs) to NICE were assessed for any additional studies [see *Appendix 3* for a critique of the clinical effectiveness section of the MS, and *Chapter 5* (*Review of manufacturers' submissions*) for further discussion of the cost-effectiveness section]. Experts who were contacted for advice and peer review were also asked to identify additional published and unpublished references. All search results were downloaded into a REFERENCE MANAGER (Thomson Reuters, New York, NY, USA) database.

Key hepatitis C websites and symposia were also searched for completed or ongoing studies and background resources. These included:

- European Association for the Study of the Liver (EASL)
- British Association for the Study of the Liver (BASL)
- American Association for the Study of Liver Diseases (AASLD)
- British Viral Hepatitis Group (BVHG)
- British Liver Trust
- British Society of Gastroenterology (BSG)
- International HIV and Hepatitis Co-infection workshop
- Health Protection Agency
- Hepatitis C Trust.

Inclusion process

Titles and abstracts identified by the search strategy for the clinical effectiveness section of the review were assessed for possible eligibility by one reviewer using an inclusion worksheet (see *Appendix 4*) based on the inclusion/exclusion criteria detailed below. The full texts of relevant papers were then obtained and inclusion criteria were applied independently by two reviewers. Any disagreements over eligibility were resolved by consensus. References identified from our previous searches were rescreened according to the inclusion criteria for the current review.

Titles and abstracts identified by the search strategy for the cost-effectiveness section of the review were assessed for potential eligibility by two reviewers independently. Economic evaluations were considered for inclusion if they reported both health service costs and effectiveness, or presented a systematic review of such evaluations. Full papers were formally assessed for inclusion by two reviewers independently. Data extraction was undertaken by one reviewer and checked by a second.

Inclusion criteria

Study design

Randomised controlled trials were included for the clinical effectiveness review. Trials published as abstracts or conference presentations from 2007 onwards were included only if sufficient details were presented to allow an appraisal of the methodology and the assessment of results to be undertaken. Systematic reviews were used only as a source of references. For the systematic review of cost-effectiveness, studies were eligible for inclusion if they reported the results of full economic evaluations [cost-effectiveness analyses (reporting cost per life-year gained), cost–utility analyses or cost–benefit analyses]. For studies reporting QoL and epidemiology/natural history, a range of study designs were eligible (e.g. cohort studies, cross-sectional surveys).

Interventions

- Combination therapy comprising ribavirin and either peginterferon alfa-2a or peginterferon alfa-2b.
- Peginterferon alfa-2a or peginterferon alfa-2b monotherapy (for patients who are unable to tolerate or are contraindicated to ribavirin).

Comparators

For patients who have been previously treated with combination therapy, and for HCV/HIV co-infected patients:

- BSC (e.g. symptomatic treatment, monitoring, treatment without any form of interferon therapy).

For patients who meet the criteria for receiving shortened courses of combination therapy:

- standard-duration courses of peginterferon alfa and ribavirin combination therapy (up to 24 or 48 weeks, as appropriate).

Population

Adults with chronic HCV, restricted to people who:

- have been previously treated with peginterferon alfa and ribavirin in combination but who relapsed/did not respond
- have HCV/HIV co-infection
- meet the criteria within the marketing authorisation for receiving shortened courses of peginterferon alfa and ribavirin in combination, namely patients with:
  - genotype 2 or 3 with LVL* at the start of treatment and an RVR (defined as HCV RNA undetectable by week 4) – shortened course of 16 weeks†
  - genotype 1 with LVL* and an RVR (defined as HCV RNA undetectable by week 4 and at week 24) – shortened course of 24 weeks
  - genotype 4 with an RVR (defined as HCV RNA undetectable by week 4 and at week 24) – shortened course of 24 weeks.†

(*For peginterferon alfa-2a, LVL is defined as ≤ 800,000 IU/ml;[42] for peginterferon alfa-2b, LVL is defined as ≤ 600,000 IU/ml.[43] †Applies only to peginterferon alfa-2a.)

Outcomes

Studies had to report SVR (defined as undetectable HCV RNA at least 6 months after treatment cessation). The following outcomes were also included:

- virological response (e.g. during treatment)
- biochemical response (e.g. ALT levels)
- histological improvement (fibrosis and inflammation)
- survival
- adverse effects of treatment
- HRQoL
- cost-effectiveness (incremental cost per life-year gained) or cost–utility [incremental cost per quality-adjusted life-year (QALY) gained].

Data extraction and critical appraisal strategy

Data from included studies were extracted by one reviewer using a standardised data extraction form and checked by a second reviewer. The quality of included RCTs was assessed using criteria recommended by CRD[49] (see *Appendix 5*). Quality criteria were applied by one reviewer and checked by a second reviewer. At each stage, any differences in opinion were resolved through discussion.

Methods of data analysis/synthesis

Data were synthesised through a narrative review with tabulation of results of all included studies. Full data extraction forms are presented in *Appendix 6*. It was not considered appropriate

to combine the RCTs in a meta-analysis owing to differences in the drug regimens and also because the population of interest (i.e. patients with LVL and RVR) were often subgroups of the main treatment arms. Any meta-analyses would therefore compromise intention-to-treat (ITT) principles and the data may be biased and not valid.

Consideration was given to performing a pairwise indirect comparison of peginterferon alfa with or without ribavirin with a trial featuring no active treatment (analogous to BSC). For this to be possible, an RCT featuring an arm in which patients were treated with peginterferon alfa would be required, in addition to an RCT featuring a 'no active treatment' (e.g. placebo) in patients with HCV/HIV co-infection or previous non-responders or relapsers. A comparator arm common to both RCTs would be necessary, such as non-peginterferon alfa. However, as will be discussed in the following chapter, we did not identify any such studies from our database of RCTs of both peginterferon and non-peginterferon alfa (which we have amassed from our previous technology assessment reports on antiviral treatment for hepatitis C for NICE since 2000). Furthermore, none of the systematic reviews of HCV/HIV co-infected patients identified in our search identified any trials in which a non-active treatment arm was included.[50,51]

As antiviral treatment for HCV has been available for some time – first with interferon alfa monotherapy, followed by the addition of ribavirin as combination therapy, and latterly with the introduction of peginterferon alfa and ribavirin – it is unlikely that any studies, whether randomised or not, will have included a non-active treatment arm, as withholding treatment would not be considered ethical.

Chapter 4

Clinical effectiveness

Results

Quantity and quality of research available

Literature searches identified 1317 references, after the removal of duplicates. A further 1389 references identified from searches conducted for our previous hepatitis C technology assessment reports[17,44] were screened according to the inclusion criteria for the present review. After further de-duplication, the total number of records screened was 2400. Following initial screening of titles and abstracts, 2310 references were excluded because they did not meet the inclusion criteria and full copies of 90 articles were retrieved. Of these, 82 were excluded on further inspection, leaving eight included studies. The total number of published papers included at each stage of the systematic review is shown in the flow chart in *Figure 1*; the list of excluded studies can be seen in *Appendix 7*.

Eight publications describing six RCTs met the inclusion criteria of the review.[52–59] Two of the articles were abstracts[57,58] linked to full publications.[53,60] All of the included studies report peginterferon and ribavirin combination therapy in patients eligible for shortened treatment duration (i.e. those with specific genotypes as described in *Chapter 3*, Inclusion crtieria). No RCTs comparing peginterferon alfa with or without ribavirin compared with BSC for the other two population groups specified in the NICE scope (i.e. re-treatment following previous non-response or relapse, and HCV/HIV co-infection) were identified through our searches. A number of RCTs comparing peginterferon alfa with or without ribavirin to active treatment comparators were identified (e.g. peginterferon alfa and ribavirin vs non-peginterferon alfa and ribavirin)

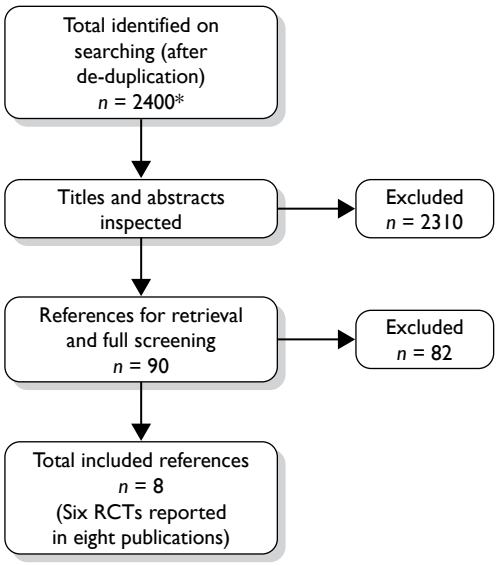

FIGURE 1 Flow chart of identification of studies for inclusion in the review. *Includes total number of studies identified in updated searches and searches from previous hepatitis C assessment reports ($n = 2706$); further de-duplication left $n = 2400$ for screening.

but these did not meet the inclusion criteria for the review, which was based on the scope of the appraisal issued by NICE.[61]

The remainder of this chapter describes the six trials in patients who were eligible for shortened courses of treatment.

Description of the included trials

The key characteristics of the RCTs are shown in *Table 1*. Four of the included studies evaluated peginterferon alfa-2a in combination with ribavirin,[53–56] one trial (Berg and colleagues[59]) evaluated peginterferon alfa-2b and ribavirin, and one trial evaluated peginterferon alfa-2a or peginterferon alfa-2b in combination with ribavirin (Mangia and colleagues[52]). The comparator in all the studies was the same intervention for a shorter duration. The dose of peginterferon alfa-2a was the same in all the trials (180 µg/week, subcutaneously), as was the dose of peginterferon alfa-2b (1.5 µg/kg/week). Ribavirin was administered orally, according to body weight, at a dose of 1000 mg/day for patients weighing ≤ 75 kg and 1200 mg/day for patients weighing > 75 kg in four studies,[52–55] or 800 mg/day for patients weighing ≤ 65 kg, 1000 mg/day for patients weighing 65–85 kg, and 1200 mg/day for patients weighing > 85 kg in one study.[56] Berg and colleagues[59] reported only that patients received 800–1400 mg/day ribavirin and it is assumed that the dose was administered according to body weight. It should be noted that in two trials,[55,56] the doses of ribavirin used are higher than those stipulated in the current licence for peginterferon alfa-2a and ribavirin combination treatment (800 mg/day for genotype 2/3[42,62]) owing to changes in the licence since these studies were carried out.

Four trials evaluated treatment in patients with genotype 1,[52–54,59] with two of these[53,54] comparing the standard 48 weeks' treatment duration with a shorter 24 weeks' treatment duration. The other two genotype 1 studies[52,59] randomised patients to the standard 48 weeks' treatment duration or to a variable treatment duration based on the time when HCV RNA first became undetectable. In the Mangia and colleagues trial,[52] patients who were first HCV RNA negative at weeks 4, 8 and 12 were treated for 24, 48 and 72 weeks, respectively; in the Berg and colleagues trial,[59] time to first HCV RNA negativity was multiplied by a factor of 6, such that patients who were first HCV RNA negative at weeks 3, 4, 5, 6, 7 or 8 were treated for 18, 24, 30, 36, 42 or 48 weeks, respectively. One trial by Yu and colleagues[55] assessed treatment in patients with genotype 2, comparing the standard 24 weeks' treatment duration with a shorter 16 weeks' treatment duration. The sixth trial by von Wagner and colleagues[56] evaluated treatment in patients with genotypes 2 and 3 and had three treatment arms. All patients were treated with combination therapy for an initial period of 8 weeks, and those with an RVR at week 4 were randomised (at week 8) to receive either a further 8 or 16 weeks' treatment (giving a total treatment duration of 16 vs 24 weeks, respectively). Patients without an RVR at week 4 were allocated (at week 8) to receive a further 16 weeks' treatment (giving a total treatment duration of 24 weeks).

In five of the RCTs,[53–56,59] patients had LVL at baseline (based on the mean viral load) ranging from 4.98 $\log_{10}$ HCV RNA (95,500 IU/ml) to 5.8 $\log_{10}$ HCV RNA (631,000 IU/ml). In the trial by Mangia and colleagues,[52] only 24% of patients were reported to have LVL (HCV RNA < 400,000 IU/ml) at baseline. However, the study was included because results were reported for the subgroup of patients with LVL and RVR. The two trials of genotype 2/3 patients[55,56] used a cut-off HCV RNA level of ≤ 800,000 IU/ml to differentiate LVL and high viral load. The Berg and colleagues trial[59] in genotype 1 patients also used a cut-off of < 800,000 IU/ml, although it should be noted that this threshold for LVL is higher than the threshold of < 600,000 IU/ml specified in the SPC for peginterferon alfa-2b.[43] Two of the trials in genotype 1 patients[52,54] used a cut-off of < 400,000 IU/ml. The sixth genotype 1 trial (Liu and colleagues[53]) presented results for viral load of between 400,000 and 1,000,000 IU/ml, at 200,000 IU/ml intervals, but in the published paper the authors appear to use a cut-off of < 800,000 IU/ml to define LVL. The trials varied in their

TABLE 1 Key characteristics of included trials ordered by genotype

Study	Methods	Key inclusion criteria	Key patient characteristics	Outcomes
Berg and colleagues 2009[59]	*Design*: open-label, multicentre RCT *No. of centres*: 19 *Country*: Germany *Sponsor*: Essex Pharma (subsidiary of Schering-Plough), Bayer Diagnostics, German Competence Network for viral hepatitis *Interventions*: PEG α-2b + RBV for 48 weeks vs PEG α-2b + RBV for 18, 24, 30, 36, 42 or 48 weeks *Follow-up*: 24 weeks after treatment cessation *No. of participants*: *n* = 433	*Inclusion criteria*: Treatment-naive adults with compensated chronic HCV, genotype 1 Anti-HCV positive HCV RNA > 1000 IU/ml by quantitative reverse transcription PCR Increased ALT levels at screening Liver biopsy consistent with chronic HCV within preceding 24 months Neutrophils ≥ 1500 µl Platelets ≥ 80,000 µl Hb ≥ 12 g/dl for women, ≥ 13 g/dl for men Creatinine < 1.5 mg/dl	Mean viral load (log_{10} IU/ml): 5.7 Group 1, 5.7 Group 2 Mean serum ALT × ULN, IU/l: 2.6 Group 1, 2.6 Group 2 Fibrosis score 0–2: 87% Group 1, 85% Group 2 Genotype 1: 100% Mean age: 42 years Gender: 55% male Mode of infection: NR Ethnicity: NR	*Primary outcome*: SVR *Secondary outcomes*: Biochemical response[a] On-treatment virological response (RVR, EOT) Relapse rate Adverse events
Mangia and colleagues 2008[52]	*Design*: multicentre RCT *No. of centres*: 11 *Country*: Italy *Sponsor*: NR *Interventions*: PEG α-2a or PEG α-2b + RBV for 48 weeks vs PEG α-2a or PEG α-2b + RBV for 24, 48 or 72 weeks *Follow-up*: 24 weeks after treatment cessation *No. of participants*: *n* = 696	*Inclusion criteria*: Treatment-naive adults with compensated chronic HCV, genotype 1 HCV RNA positive Anti-HCV positive Neutrophils ≥ 1500 µl Platelets ≥ 90,000 µl Hb ≥ 12 g/dl for women, ≥ 13 g/dl for men Creatinine < 1.5 mg/dl	Serum HCV RNA < 400,000 IU/ml: 26% Group 1, 22% Group 2 Serum ALT ≥ 3 ULN: 19% Group 1, 16% Group 2 Fibrosis score 0–2: 62% Group 1, 65% Group 2 Genotype 1a: 9%, 1b: 91% Mean age: 52 years Gender: 56% male Mode of infection: blood transfusion 21%, drug abuse 7%, unknown 72% Ethnicity: NR Treatment: PEG α-2a 46% Group 1, 49% Group 2; PEG α-2b 53% Group 1, 51% Group 2	*Primary outcome*: SVR *Secondary outcomes*: RVR EOT virological response SVR according to virological response at weeks 4, 8 and 12 Relapse rate Adverse events
Liu and colleagues 2008;[53] 2008 abstract[57]	*Design*: multicentre RCT *No. of centres*: 5 *Country*: Taiwan *Sponsor*: National Taiwan University Hospital, National Science Council & Department of Health, Executive Yuan, Taiwan *Interventions*: PEG α-2a + RBV for 24 weeks vs PEG α-2a + RBV for 48 weeks *Follow-up*: 24 weeks after treatment cessation *No. of participants*: *n* = 308	*Inclusion criteria*: Treatment-naive adults with chronic HCV, genotype 1 Liver biopsy consistent with chronic HCV within previous 3 months Detectable HCV RNA for > 6 months Presence of anti-HCV antibody Serum ALT > ULN	Mean viral load (log_{10} IU/ml): 5.7 Group 1, 5.8 Group 2 Mean serum ALN × ULN: 3.2 Group 1, 3.0 Group 2 Fibrosis score ≥ 3: 77% Genotype 1a: 2%, 1b: 94%, 1a and 1b: 4% Mean age: 54 years Gender: 57% male Mode of infection: NR Ethnicity: 100% Asian	*Primary outcome*: SVR *Secondary outcomes*: RVR EVR EOT virological response Relapse rate Biochemical response Histological response Adverse events

continued

TABLE 1 Key characteristics of included trials ordered by genotype *(continued)*

Study	Methods	Key inclusion criteria	Key patient characteristics	Outcomes
Yu and colleagues 2008;[54] 2007 abstract[58]	*Design*: open-label, multicentre RCT *No. of centres*: 4 *Country*: Taiwan *Sponsor*: Taiwan Liver Research Foundation *Interventions*: PEG α-2a + RBV for 24 weeks vs PEG α-2a + RBV for 48 weeks *Follow-up*: 24 weeks after treatment cessation *No. of participants*: *n* = 200	Treatment-naive adults with chronic HCV, genotype 1 Liver biopsy consistent with chronic HCV within ≤1 year of study entry HCV RNA positive Positive for HCV antibodies Elevated serum ALT ≥2 measurements within ≤6 months of study entry Neutrophils ≥1500 mm^{-3} Platelets ≥90,000 µl Hb >12 g/dl for women, >11 g/dl for men Creatinine <1.5 mg/dl	Mean viral load (log_{10} IU/ml): 5.43 Group 1, 5.66 Group 2 Serum HCV RNA <400,000 IU/ml: 55% Serum ALT IU/l: 156 Group 1, 137 Group 2 Fibrosis score 0–2: 75% Group 1, 81% Group 2 Genotype 1: 100% Mean age: 49 years Gender: 57% male Mode of infection: NR Ethnicity: NR	*Primary outcome*: SVR *Secondary outcomes*: RVR EVR EOT virological response Relapse rate Adverse events
Yu and colleagues 2007[55]	*Design*: open-label, multicentre RCT *No. of centres*: 4 *Country*: Taiwan *Sponsor*: Taiwan Liver Research Foundation *Interventions*: PEG α-2a + RBV for 24 weeks vs PEG α-2a + RBV for 16 weeks *Follow-up*: 24 weeks after treatment cessation *No. of participants*: *n* = 150	Treatment-naive adults with chronic HCV, genotype 2 Liver biopsy consistent with chronic HCV within ≤1 year of study entry Seropositive for HCV RNA Seropositive for HCV antibodies Increased serum ALT ≥1.5 × ULN for ≤2 measurements within 6 months before study entry Neutrophils >1500 mm^{-3} Platelets >9×10^4 mm^{-3} Hb >12 g/dl for women, >11 g/dl for men Creatinine <1.5 mg/dl	Mean viral load (log_{10} IU/ml): 4.88 Group 1, 4.98 Group 2 Serum ALT IU/l: 108.9 Group 1, 107 Group 2 Fibrosis score 0–2: 80% Group 1, 78% Group 2 Genotype 2: 100% Mean age: 50 years Gender: 60% male Mode of infection: NR Ethnicity: 100% Asian (Taiwanese)	*Primary outcome*: SVR *Secondary outcomes*: RVR EOT virological response Relapse rate Adverse events
von Wagner and colleagues 2005[56]	*Design*: multicentre, Phase IIIb RCT *No. of centres*: 6 *Country*: Germany *Sponsor*: Hoffmann-La Roche and German Hepatitis Network of Competence (Hep-Net) *Interventions*: PEG α-2a + RBV for 16 weeks vs PEG α-2a + RBV for 24 weeks (RVR) vs PEG α-2a + RBV for 24 weeks (no RVR) *Follow-up*: 24 weeks after treatment cessation *No. of participants*: *n* = 142	Treatment-naive adults with compensated chronic HCV, genotype 2 or 3 Liver biopsy consistent with chronic HCV within ≤18 months before study entry HCV RNA positive (>600 IU/ml) Positive for anti-HCV antibodies Elevated serum ALT at screening or study entry Neutrophils >1500/µl Platelets >90,000/µl Hb ≥12 g/dl for women, ≥13 g/dl for men	Mean viral load (log_{10} IU/ml): 5.8 Group 1, 5.8 Group 2 Serum ALT × ULN IU/l: 2.8 Group 1, 2.8 Group 2 Mean fibrosis score: 1.6 Group 1, 1.6 Group 2 Genotype 2: 27%, genotype 3: 73% Mean age: 38 years Gender: 65% male Mode of infection: NR Ethnicity: NR	*Primary outcome*: SVR *Secondary outcomes*: RVR EOT virological response Biochemical response Adverse events

ALT, alanine aminotransferase; EOT, end-of-treatment; EVR, early virological response; HCV, hepatitis C virus; IU, international unit; NR, not reported; PEG α, peginterferon alfa; RBV, ribavirin; RCT, randomised controlled trial; RVR, rapid virological response; SVR, sustained virological response; ULN, upper limit of normal.

a Reported by the authors as a secondary outcome but results not presented in the publication.

lower limits of detection of serum HCV RNA. For RVR, a lower limit of < 50 IU/ml was used in three trials,[52,54,55] < 25 IU/ml was used in one trial,[53] < 600 IU/ml in one trial[56] and < 615 IU/ml in the sixth trial.[59] For SVR, most of the trials had a threshold of < 50 IU/ml,[52,54–56] whereas Liu and colleagues[53] used a lower limit of < 25 IU/ml. In the Berg and colleagues trial,[59] HCV RNA negativity was verified using a highly sensitive transcription-mediated amplification (TMA) assay with a detection limit of < 5.3 IU/ml.

All of the included studies were multicentre trials (ranging from 4 to 19 centres), recruiting patients from medical centres, hospitals and/or tertiary referral centres in Taiwan,[53–55] Italy[52] and Germany.[56,59] The trial by Mangia and colleagues[52] was the largest, recruiting 696 patients, followed by Berg and colleagues ($n = 433$)[59] and Liu and colleagues ($n = 308$).[53] The numbers of participants in the three smaller trials ranged from 142 to 200. Two of the studies received partial funding from the drug manufacturers: von Wagner and colleagues[56] were partially sponsored by Hoffmann-La Roche, and Berg and colleagues[59] were partially sponsored by Essex Pharma (a subsidiary of Schering-Plough).

All of the trials were based on middle-aged (mean age range 39–53 years) adult patients, with the proportion of male participants ranging from 55% to 73%. Patients were treatment naive in all studies. Two of the studies[53,55] reported that 100% of patients were of Asian ethnicity, and it can be assumed that this was also the case for the third Taiwanese study.[54] The ethnicity groups of the three European studies[52,56,59] were not reported. Only one trial[52] reported the source of infection, although for nearly three-quarters of patients this was unknown: approximately 20% were infected by blood transfusion and 7% via intravenous drug use. The proportion of patients with a fibrosis score of 0–2 was similar in four trials[52,54,55,59] (range 62%–87%), with one-fifth[56] reporting a mean fibrosis score of 1.6. In contrast, more than three-quarters of patients in the study by Liu and colleagues[53] had a fibrosis score of ≥ 3, indicating a greater degree of liver damage.

In general, all six trials had similar inclusion criteria, with patients required to have chronic HCV (as determined by liver biopsy in five trials[53–56,59]), be positive for anti-HCV antibodies, be HCV RNA positive and have elevated serum ALT levels.[53–56,59] The other primary inclusion criterion was a specific HCV genotype, with patients required to have HCV genotype 1,[52–54,59] genotype 2[55] or genotype 2 or 3.[56]

Exclusion criteria were similar across the included trials. All six trials excluded patients with significant comorbidities, such as chronic hepatitis B or HIV infection, autoimmune liver disease or other causes of liver disease, as well as organ transplant, excessive alcohol intake or pregnancy. All except one study[52] excluded patients with psychiatric conditions, and four studies[52,53,56,59] excluded patients with drug abuse. Further details on exclusion criteria can be found in the data extraction forms in *Appendix 6*.

All of the trials stipulated certain laboratory readings in their inclusion/exclusion criteria, most of which are related to conditions that are consistent with decompensated liver cirrhosis, such as thrombocytopenia, anaemia and neutropenia. Patients were required to have a neutrophil count of > 1500 cells/mm^3, a platelet count ranging from at least 70,000 cells/mm^3 to at least 90,000 cells/mm^3, haemoglobin (Hb) levels of ≥ 11–12 g/dl for women and ≥ 12–13 g/dl for men, and creatinine level of < 1.5 mg/dl.[53–55,59,63]

All six RCTs reported SVR as the primary outcome measure. In terms of secondary outcomes, RVR and end-of-treatment (EOT) virological response were reported by all six trials, with some trials also reporting EVR at week 12 of therapy[53,54] and relapse rate.[53–55,59] Biochemical response (ALT levels) was reported by two trials[53,56] and histological response by one trial.[53] Five

RCTs[52–54,56,59] presented SVR rates according to RVR and viral load. All six trials reported adverse events in some way but none reported HRQoL.

Characteristics for the third treatment arm in the von Wagner and colleagues trial[56] are not discussed here, as this group did not achieve an RVR and thus is not relevant to this review. It is not possible to report baseline characteristics for the 24-week subset of the variable treatment duration groups in the trials by Mangia and colleagues[52] and Berg and colleagues,[59] as these were not reported separately by the authors.

Quality assessment of included studies

The methodological quality of reporting in the included studies was assessed using criteria set by CRD at the University of York,[49] and is shown in *Table 2*. On the whole, the methodological quality of the trials was good, particularly for the two studies by Yu and colleagues.[54,55] Four trials explicitly reported a computer-generated randomisation procedure that assured true random assignment to treatment groups, while in two studies[56,59] details were not reported. The use of a central randomisation procedure assured adequate concealment of allocation in only two trials.[54,55]

The groups appeared similar at baseline on demographic, biochemical and virological characteristics, with most presenting supporting statistical comparisons. However, in the studies by Berg and colleagues[59] and Mangia and colleagues,[52] the comparability of the standard-treatment-duration group (48 weeks) versus the 24 weeks' subset of the variable-treatment-duration group is unknown, as characteristics for this subset were not presented. Neither patients nor caregivers were blinded to treatment in any of the trials, but this would not be possible given the treatment regimens. Although the blinding of outcome assessors was unclear in all trials, the possibility of detection bias would be minimal, given the objective hard end point of virological response.

There were no unexpected imbalances in dropouts between groups in any of the studies, nor was there any evidence to suggest that the authors measured more outcomes than they reported, with the exception of the Berg and colleagues study,[59] where sustained biochemical response was reported by the authors as a secondary outcome but no results were presented in the publication. All six RCTs undertook an appropriate ITT data analysis for the primary efficacy outcome, although appropriate methods were used to account for missing data in only

TABLE 2 Quality assessment of included trials

Quality criteria	Berg 2009[59]	Mangia 2008[52]	Liu 2008[53]	Yu 2008[54]	Yu 2007[55]	von Wagner 2005[56]
Adequate randomisation	Unclear	Yes	Yes	Yes	Yes	Unclear
Adequate allocation concealment	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Similarity of baseline prognostic factors	Yes[a]	Yes[a]	Yes	Yes	Yes	Yes
Blinding of outcome assessors	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Blinding of care provider	No	No	No	No	No	No
Blinding of patient	No	No	No	No	No	No
Unexpected imbalances in dropouts	No	No	No	No	No	No
More outcomes measured than reported	Yes	No	No	No	No	No
ITT analysis included:	Yes	Yes	Yes	Yes	Yes	Yes
Appropriate	Unclear	Yes	Yes	Yes	Yes	Yes
Missing data accounted for	Unclear	Unclear	Unclear	Yes	Yes	Yes

a Baseline characteristics similar for group 1 vs group 2 as a whole, but unclear for group 1 vs 24-week subset.

three trials.[54–56] All of the trials were statistically powered (at 80%) for the primary outcome of SVR between treatment groups as a whole. However, none performed a power calculation for patient subgroups (such as those with RVR and LVL), and therefore these results in the following sections should be interpreted with caution.

Assessment of clinical effectiveness

The results in the following sections relate to the included trials of patients eligible for shortened courses of treatment with the focus on the subgroup of patients with an RVR and LVL, where reported. Results presented in the tables are ordered by genotype.

Sustained virological response

Sustained virological response was defined as undetectable serum HCV RNA (< 50 IU/ml,[52,56] 25 IU/ml,[53] < 5.3 IU/ml[59]) at the end of 24 weeks' follow-up in four trials, and as HCV RNA negative (< 50 IU/ml) at the end of treatment and end of follow-up in two trials.[54,55]

Sustained virological response was the primary outcome in all six included RCTs. Four of the trials[52–54,56] separately reported SVR in the subgroup of patients who achieved an RVR and had LVL at baseline, which is the patient subgroup meeting the licensed criteria for receiving shortened courses of combination therapy (*Table 3*). Yu and colleagues[55] reported SVR for patients who achieved an RVR, but did not further stratify this subset by baseline viral load. However, it can be assumed that rates would be similar to SVR by RVR rates, as the mean baseline viral load was low for both treatment arms, and approximately 83% of the study population had LVL at baseline (< 800,000 IU/ml). Although the trial by Berg and colleagues[59] reported SVR in the subgroup of patients who achieved an RVR and had LVL at baseline, the threshold used was either ≤ 800,000 IU/ml or > 800,000 IU/ml, which differs from the threshold of < 600,000 IU/ml specified in the SPC for the study drug peginterferon alfa-2b.[43] For this reason we do not present the results for this subgroup, but instead present the SVRs for the subgroup that achieved an RVR irrespective of the baseline viral load. As the mean viral load for the study sample, as a whole, was $\log_{10}$ 5.7 IU/ml (calculated to be around 500,000 IU/ml), these SVRs can be considered, overall, to reflect LVL in accordance with the SPC.

Results for SVR for treatment groups as a whole, SVR by RVR, and SVR by viral load can be seen in the data extraction forms in *Appendix 6*.

In patients with LVL (≤ 800,000 IU/ml) who attained an RVR, SVR rates were comparable between groups who received the standard duration of treatment and those who received shortened courses, for both genotype 1 and genotypes 2 and 3. Rates were similar in five trials, ranging from 83% to 100% for standard treatment duration compared with 84%–96% for shortened treatment duration, with no statistically significant differences between treatment arms. In addition, SVRs were broadly similar regardless of genotype with the exception of the trial by Berg and colleagues,[59] in which SVRs were lower than in the other studies. This may be due to the fact that these rates are only for those who first became HCV RNA negative at week 4 and do not include those who became HCV RNA negative during weeks 1–3 (as a consequence of the study design), whereas in all of the other trials the rates reflect all patients who became negative up to week 4. It should also be noted that patient numbers in these subgroups were small, and none of the trials was powered for this subgroup analysis. In the trial by Mangia and colleagues,[52] in particular, only 10% of patients had an RVR and LVL.

For those with high baseline viral load, lower SVR rates were observed in patients who were treated for a shorter duration, although this was reported to be statistically significant in only two trials (100% vs 92%, $p = 0.03$, at < 1,000,000 IU/ml;[53] 100% vs 76.5% , $p = 0.045$, at ≥ 400,000 IU/ml[54] for standard vs shortened treatment, respectively).

TABLE 3 Sustained virological response in the subgroup of patients with an RVR and LVL

Study details		Group 1	Group 2	*p*-value
Genotype 1				
Berg and colleagues 2009[59]		**PEG α-2b + RBV[a]**	**PEG α-2b + RBV**	
		48 weeks, *n* = 225	**24 weeks, *n* = 28[b]**	
SVR by RVR, % (*n*/*N*)		42 (8/19)	57 (16/28)	NR
Mangia and colleagues 2008[52]		**PEG α-2a or α-2b + RBV**	**PEG α-2a or α-2b + RBV**	
		48 weeks, *n* = 237	**24 weeks, *n* = 123[c]**	
SVR by RVR and baseline viral load,% (*n*/*N*)	< 400,000 IU/ml	83.3 (20/24)	84.4 (38/45)	0.83
	≥ 400,000 IU/ml	86.8 (33/38)	73.1 (57/78)	0.14
Liu and colleagues 2008[53]		**PEG α-2a + RBV**	**PEG α-2a + RBV**	
		48 weeks, *n* = 154	**24 weeks, *n* = 154**	
SVR by RVR and baseline viral load,% (*n*)	< 400,000 IU/ml	100 (42)	94 (49)	0.25
	< 600,000 IU/ml	100 (50)	93 (61)	0.13
	< 800,000 IU/ml	100 (57)	94 (69)	0.13
	< 1,000,000 IU/ml	100 (61)	92 (71)	0.03
Yu and colleagues 2008[54]		**PEG α-2a + RBV**	**PEG α-2a + RBV**	
		48 weeks, *n* = 100	**24 weeks, *n* = 100**	
SVR by RVR and baseline viral load, % (*n*/*N*)	< 400,000 IU/ml (*n* = 52)	100 (24/24)	96.4 (27/28)	1.000[d]
	≥ 400,000 IU/ml (*n* = 35)	100 (18/18)	76.5 (13/17)	0.045
Genotype 2/3				
Yu and colleagues 2007[55]		**PEG α-2a + RBV**	**PEG α-2a + RBV**	
		24 weeks, *n* = 100	**16 weeks, *n* = 50**	
SVR by RVR, % (*n*/*N*)	RVR	98 (85/87)	100 (43/43)	1
	No RVR	77 (10/13)	57 (4/7)	0.610
von Wagner and colleagues 2005[56]		**PEG α-2a + RBV**	**PEG α-2a + RBV**	
		24 weeks, RVR *n* = 71[e]	**16 weeks, RVR *n* = 71[e]**	
SVR by RVR and baseline viral load, % (*n*/*N*)	≤ 800,000 IU/ml (*n* = 66)	87 (27/31)	94 (33/35)	NR
	> 800,000 IU/ml (*n* = 75)	75 (30/40)	69 (24/35)	NR

NR, not reported; PEG α, peginterferon alfa; RBV, ribavirin.

a For subgroup of patients who first became HCV RNA negative at week 4. Results are also presented in the trial publication for a subgroup of patients who became HCV RNA negative between weeks 1 and 3. Therefore, the results presented in the table are not for all patients who were HCV negative by week 4 – only those who were first negative at that time point.

b Variable treatment arm was 18, 24, 30, 36, 42 or 48 weeks (*n* = 208), based on time when HCV RNA first became undetectable (corresponding to 3, 4, 5, 6, 7 or 8 weeks, respectively) – results for the 24-week subset only (*n* = 28) are presented here.

c Variable treatment arm was 24, 48 or 72 weeks (*n* = 459), based on time when HCV RNA first became undetectable – results for the 24-week subset only (*n* = 123) are presented here.

d Difference –3.6% [95% confidence interval (CI) –14.3 to –0.6].

e Randomised at week 8 according to RVR at week 4 – patients not achieving RVR not reported here.

Virological response during treatment

The included trials varied in their lower limits of detection, with RVR defined as undetectable serum HCV RNA (< 25 IU/ml),[53] serum HCV RNA negative (< 50 IU/ml),[52,54,55] serum HCV RNA < 600 IU/ml[56] or < 615 IU/ml,[59] all at week 4 of therapy.

Table 4 presents RVR rates for each of the six included RCTs. There were no statistically significant differences between treatment groups who received the standard duration of treatment compared with those who received shortened courses, for both genotype 1 and genotypes 2 and 3.

There was a large range in reported RVR between the studies, with rates in genotype 1 patients generally being lower than in genotype 2/3 patients. In the four genotype 1 trials,[52–54,59] 26%–68% of patients achieved an RVR, although in the subset of patients treated for 24 weeks in the Mangia and colleagues trial[52] all of the patients achieved an RVR as per the study design (see *Description of the included trials*). The rates in this trial were lower than in the other five trials,

TABLE 4 Rapid virological response

Study details	Group 1	Group 2	*p*-value
Genotype 1			
Berg and colleagues 2009[59]	**PEG α-2b + RBV**	**PEG α-2b + RBV**	
	48 weeks, *n* = 225	**24 weeks, *n* = 28[a]**	
Percentage with response (*n*/*N*):[b] RVR	8.4 (19/225)[c]	13.5 (28/208)[c]	NR
	35 (78/225)[d]	37 (76/208)[d]	
Mangia and colleagues 2008[52]	**PEG α-2a or α-2b + RBV**	**PEG α-2a or α-2b + RBV**	
	48 weeks, *n* = 237	**24 weeks, *n* = 123[e]**	
Percentage with response (*n*/*N*): RVR	26.2 (62/237)	26.8 (123/459)[f]	0.90
		100 (123/123)[g]	
Liu and colleagues 2008[53]	**PEG α-2a + RBV**	**PEG α-2a + RBV**	
	48 weeks, *n* = 154	**24 weeks, *n* = 154**	
Percentage with response (*n*): RVR	63 (97)	68 (104)	0.47
Yu and colleagues 2008[54]	**PEG α-2a + RBV**	**PEG α-2a + RBV**	
	48 weeks, *n* = 100	**24 weeks, *n* = 100**	
Percentage with response (*n*): RVR	42	45	NR
Genotype 2/3			
Yu and colleagues 2007[55]	**PEG α-2a + RBV**	**PEG α-2a + RBV**	
	24 weeks, *n* = 100	**16 weeks, *n* = 50**	
Percentage with response (*n*/*N*): RVR	87 (87/100)	86 (43/50)	NR
von Wagner and colleagues 2005[56]	**PEG α-2a + RBV**	**PEG α-2a + RBV**	**PEG α-2a + RBV**
	24 weeks, RVR *n* = 71[h]	**16 weeks, RVR *n* = 71[h]**	**24 weeks, no RVR, *n* = 11[h]**
Percentage with response: RVR	100	100	0 NR

PEG α, peginterferon alfa; RBV, ribavirin.

a Variable treatment arm was 18, 24, 30, 36, 42 or 48 weeks (*n* = 208), based on time when HCV RNA first became undetectable (corresponding to 3, 4, 5, 6, 7 or 8 weeks, respectively) – results for the 24-week subset only (*n* = 28) are presented here.

b Percentages calculated by reviewer from numbers presented in trial publication.

c Rates are for the subgroup of patients who became HCV RNA negative at week 4 only (not including those who became first negative between weeks 1 and 3).

d We have combined the total number of patients first becoming HCV RNA negative between weeks 1 and 3 (*n* = 59 in Group 1, *n* = 48 in Group 2) with those becoming first negative at week 4 (*n* = 19 in Group 1, *n* = 28 in Group 2) to ensure that figures are comparable with the other studies in this table.

e Variable treatment arm was 24, 48 or 72 weeks (*n* = 459), based on time when HCV RNA first became undetectable – the 24-week subset only (*n* = 123) is presented here.

f For all of variable treatment group (*n* = 459).

g In those who achieved an RVR.

h Randomised at week 8 according to RVR at week 4.

and this may be due to the smaller proportion of patients (24%) having LVL at baseline. In the trial of genotype 2 patients by Yu and colleagues,[55] rates were much higher at 86%. In the study of genotype 2/3 patients,[56] two of the three treatment arms had RVR rates of 100% owing to the nature of the study design, whereby patients who achieved an RVR at week 4 were randomised (at week 8) to a total of 16 or 24 weeks' treatment. In the trial by Mangia and colleagues,[52] it is also reported that RVR rates were not significantly different between those treated with peginterferon alfa-2a compared with peginterferon alfa-2b (24% vs 29%, respectively, $p = 0.14$) (see *Appendix 6*), although results were not reported for the different treatment arms for the two peginterferons.

Early virological response rates and EOT response rates were similar for patients receiving shortened and standard duration treatment, with no statistically significant differences (where significance values were reported). As these results were presented for all patients rather than the subgroup of patients with RVR and LVL of interest to this systematic review, we have not presented these data here. However, for information they can be found in *Appendix 6*.

Relapse rate

Relapse was defined as the re-appearance of serum HCV RNA during the 24-week follow-up period in patients who achieved an EOT response. The RCT by Yu and colleagues[54] was the only included trial to report the relapse rate in the subgroup of patients with an RVR and LVL (*Table 5*). In this subgroup, rates of relapse were low and were not statistically significantly different between treatment arms [3.6% vs 0% for 24 vs 48 weeks, respectively, difference 3.6%, 95% confidence interval (CI) −7.2 to 6.6, $p = 1.000$]. In those with an RVR and high viral load, shortening the duration of therapy resulted in higher rates of relapse, reaching statistical significance (23.5% vs 0 for 24 weeks vs 48 weeks, respectively, $p = 0.045$).

Relapse rates for the other included RCTs can be found in *Appendix 6*. These have not been presented here because they were reported for the study groups as a whole rather than the subgroup of patients of relevance to this systematic review (i.e. those with both LVL and an RVR).

Biochemical response

Two RCTs reported biochemical response rate (normalisation of ALT levels) (*Table 6*).[53,56] In one trial of genotype 1 patients (Liu and colleagues[53]), data were analysed for 248 patients with available paired ALT levels (baseline and end of follow-up). Treatment for 24 weeks resulted in a lower ALT normalisation rate compared with 48 weeks of treatment, with the difference being statistically significant (51% vs 72%, respectively, $p < 0.001$). However, the study did not report the response rate for the subgroup of patients with an RVR or RVR and LVL. In the trial of genotype 2/3 patients (von Wagner and colleagues[56]) there was no statistically significant difference in sustained biochemical response rates between groups who achieved an RVR.

TABLE 5 Relapse rate, Yu and colleagues[54] (genotype 1)

Study details		Group 1 (PEG α-2a + RBV 48 weeks, *n* = 100)	Group 2 (PEG α-2a + RBV 24 weeks, *n* = 100)	*p*-value
Relapse rate by RVR and baseline viral load, % (*n*/*N*)	< 400,000 IU/ml (*n* = 52)	0 (0/24)	3.6 (1/28)	1.000[a]
	≥ 400,000 IU/ml (*n* = 35)	0 (0/18)	23.5 (4/17)	0.045

PEG α, peginterferon alfa; RBV, ribavirin.
a Difference 3.6% (95% CI −7.2 to 6.6).

Histological response

Histological response was reported by one trial in patients with genotype 1 HCV (Liu and colleagues[53]), and was analysed for 295 patients with available paired liver biopsy specimens (baseline and end of follow-up). However, the numbers in each treatment arm were not reported by the authors. Patients who received the shortened treatment regimen had a significantly lower histological response than those treated for the standard duration of 48 weeks (59% vs 78%, respectively, $p = 0.001$). Again, the study did not report the response rate specifically for the subgroup of patients with an RVR or RVR and LVL (*Table 7*).

Adverse events

Adverse events for the included studies are presented in *Table 8*. All of the trials presented adverse events for treatment groups as a whole, not for the subgroup of patients achieving an RVR and with LVL.

The incidence of dose discontinuations as a result of adverse events was reported by all six RCTs and was low across treatment groups, ranging from 0% to 9%. For three trials (all genotype 1[53,54,59]) there appeared to be fewer discontinuations due to adverse events in those patients treated for a shortened duration, although this was not significantly different in one trial ($p = 0.10$)[53] and not statistically tested in the other two.[54,59] However, Yu and colleagues[54] found a statistically significant difference in the total incidence of treatment discontinuations (for adverse events and other reasons combined) in favour of the shortened treatment regimen (10% vs 3%, $p = 0.045$). In the trial by von Wagner and colleagues[56] in genotype 2/3 patients, the total incidence of treatment discontinuations also appeared to favour the shortened-treatment-duration group (1% vs 8% for 16 weeks vs 24 weeks, respectively), although this was not statistically tested.

TABLE 6 Biochemical response

Study details	Group 1	Group 2	*p*-value
Genotype 1			
Liu and colleagues 2008[53]	**PEG α-2a + RBV 48 weeks**	**PEG α-2a + RBV 24 weeks**	
Percentage with response (*n*)	72 (107)	51 (75)	< 0.001
Genotype 2/3			
von Wagner and colleagues 2005[56]	**PEG α-2a + RBV 24 weeks, RVR *n* = 71**	**PEG α-2a + RBV 16 weeks, RVR *n* = 71**	
Percentage with response	87	89	NR

PEG α, peginterferon alfa; RBV, ribavirin.

TABLE 7 Histological response, Liu and colleagues[53] (genotype 1)

Study details	Group 1 (PEG α-2a + RBV 48 weeks)	Group 2 (PEG α-2a + RBV 24 weeks)	*p*-value
Percentage with response (*n*)	78 (97)	59 (71)	0.001

PEG α, peginterferon alfa; RBV, ribavirin.

TABLE 8 Adverse events

		Genotype 1								Genotype 2		Genotype 2/3	
		Berg and colleagues 2009[59] (PEG α-2b + RBV)		Mangia and colleagues 2008[52] (PEG α-2a or α-2b + RBV)		Liu and colleagues 2008[53] (PEG α-2a + RBV)		Yu and colleagues 2008[54] (PEG α-2a + RBV)		Yu and colleagues 2007[55] (PEG α-2a + RBV)		von Wagner and colleagues 2005[56] (PEG α-2a + RBV)	
Reported adverse events: % (*n*) of patients affected		**48 weeks (*n*=225)**	**Variable[a] (*n*=208)**	**48 weeks (*n*=237)**	**Variable[a] (*n*=459)**	**48 weeks (*n*=154)**	**24 weeks (*n*=154)**	**48 weeks (*n*=100)**	**24 weeks (*n*=100)**	**24 weeks (*n*=100)**	**16 weeks (*n*=50)**	**24 weeks, RVR (*n*=71)[b]**	**16 weeks, RVR (*n*=71)[b]**
Dose discontinuation:				10 (24)	13 (59)			10 (10)	3 (3)[c]	1 (1)	0	8 (6)	1 (1)
Adverse event		3 (7)	2 (4)	7 (16)	7 (30)	9 (14)	4 (6)	8 (8)	3 (3)	1 (1)	0	1 (1)	1 (1)
Other reason				3 (8)	6 (29)			2 (2)	0	0	0	7 (5)	0
Dose modification[d] for adverse events/lab abnormalities	PEG α-2a	NR	NR	NR	NR	NR	NR	24 (24)	22 (22)	9 (9)	8 (4)	19 (13)	7 (5)
	RBV	NR	NR	NR	NR	NR	NR	60 (60)	49 (49)	51 (51)	46 (23)	11 (8)	8 (6)
	PEG α-2a or RBV	NR	NR	NR	NR	NR	NR	65 (65)	54 (54)	54 (54)	52 (26)	NR	NR
	PEG α-2b or RBV	16	15	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Dose reduction for any adverse event	NR	NR	14 (32)	10 (47)	53 (82)	45 (69)	NR	NR	NR	NR	NR	NR
Serious adverse events		6.6	2.6	NR	NR	3 (4)	7 (11)	1 (1)	1 (1)	0	0	5 (7)[e]	
Deaths, *n*		NR	NR	NR	NR	1	0	NR	NR	NR	NR	NR	NR

PEG α, peginterferon alfa; RBV, ribavirin.

a Results presented for all patients in the variable treatment arm, as adverse events not reported for 24-week subset only.

b Randomised at week 8 according to RVR at week 4 – patients not achieving RVR not reported here.

c $p=0.045$.

d Dose modification or transient interruption for Yu and colleagues 2008[54] and von Wagner and colleagues[56] trials.

e Seven out of whole study population ($n=153$).

For four trials,[54–56,59] the incidence of drug dose modifications for adverse events/laboratory abnormalities [classified by the studies as either peginterferon alfa-2a, RBV (ribavirin), peginterferon alfa-2a or RBV, or peginterferon alfa-2b or RBV] was observed to be lower in patients treated for a shortened duration, as might be expected, although the differences were not statistically significant[54,55] or not tested.[56,59] The same trend was observed in the two trials that presented the incidence of drug dose reductions for any adverse event, but differences between treatment arms were not statistically tested.[52,53]

The incidence of serious adverse events was low (range 0%–7%) as reported by five trials.[53–56,59] Frequencies were not different between treatment arms although statistical tests were generally not reported. In two trials[54,56] it is not clear whether the events were related to treatment or not, although in one trial[53] 12 of the 15 events were considered to be treatment related (3 out of 4 vs 9 out of 11 in 48 weeks vs 24 weeks, respectively, $p = 0.11$). von Wagner and colleagues[56] did not differentiate between the three treatment groups when reporting this outcome, so the proportion in each group is unknown. Only one death was reported,[53] which was due to reactivation of pulmonary tuberculosis in a patient with a history of pulmonary tuberculosis and prolonged fever, dyspnoea and weight loss.

All of the trials reported the frequency of specific adverse events (see full data extractions in *Appendix 6* for more details) with the exception of Berg and colleagues,[59] who did not present the data. Most adverse events reported were typical of those commonly associated with peginterferon-based treatment. The most frequently occurring adverse events were similar across trials and included influenza-like symptoms, such as headache, fatigue and fever, insomnia, anorexia, dermatological symptoms such as skin rash/dry skin and alopecia. On the whole, the frequency of adverse events was not statistically different between treatment arms, although in three studies[53,54,56] there was a trend for a lower incidence of events in patients treated for a shorter duration. Two trials[54,55] reported statistical tests for comparison between groups for all the reported adverse events, two trials reported statistical comparisons for some adverse events,[52,53] while two trials[56,59] presented no statistical comparison between treatment groups. Liu and colleagues[53] found that body weight loss (weight reduction of > 10% from baseline weight) was encountered less frequently in those receiving treatment for 24 weeks than in those receiving treatment for 48 weeks (19% vs 30%, respectively, $p = 0.03$). In the trial by Yu and colleagues,[55] the incidence of alopecia was significantly lower in the 16-week group than in the 24-week group (20% vs 49%, respectively, $p = 0.001$).

Clinical effectiveness: summary

- All six included RCTs were in patients who were eligible for shortened treatment duration. No RCTs comparing peginterferon alfa with or without ribavirin with BSC were identified for the HCV/HIV co-infection or re-treatment patient groups.
- In the subgroup of patients who achieved an RVR and had LVL at baseline, SVR rates were comparable (i.e. no statistically significant differences) between groups who received the standard duration of treatment and those who received shortened courses, for both genotype 1 and genotypes 2 and 3. This implies that this patient group can receive shortened courses of peginterferon combination therapy without compromising SVR rates.
- For both genotype 1 and genotype 2 and 3 patients, there were no statistically significant differences in rates of RVR between treatment groups who received the standard duration of treatment and those who received shortened courses. Rates of RVR in genotype 2/3 patients were observed to be generally higher than in genotype 1 patients.
- Relapse rates in the subgroup of patients with LVL and RVR (one trial) were low and not significantly different between those treated for 24 versus 48 weeks.
- Treatment for 24 weeks resulted in a significantly lower biochemical response rate (reduction of ALT to normal levels) and histological response rate than 48 weeks of treatment in one

trial of genotype 1 patients. Shortening the treatment duration had no effect on biochemical response in one trial of genotype 2/3 patients. Rates of biochemical and histological response should be treated with caution, as the results relate only to those patients with available data and rates were not reported in the subgroup of patients with LVL and RVR.

- Adverse events were presented for treatment groups as a whole and the reporting of statistical tests varied. However, the most frequently occurring adverse events were similar across all the trials and included flu-like symptoms, insomnia, anorexia, dermatological symptoms and alopecia.
- There was a trend for a lower incidence of adverse events in patients who were treated for a shorter duration (three trials), although statistically they were comparable between treatment arms. The incidence of dose discontinuations was significantly lower in those receiving a shortened treatment regimen in one trial.
- None of the studies was powered for subgroup analysis and therefore the results should be interpreted with caution.

Ongoing studies

The following study was identified in searches and is currently ongoing:

- NCT 00532701. Peginterferon alfa-2a and ribavirin in patients with genotype 2 chronic hepatitis C: a randomised study of treatment duration and ribavirin dose stratified by rapid virological response. Study type: Phase IV, open-label, parallel RCT. Sample size: 700. Start date: June 2006. Estimated study completion date: June 2009. Status: currently recruiting participants. Funding: National Taiwan University Hospital. Funding amount: not stated.

Chapter 5

Economic analysis

The aim of this section is to assess the cost-effectiveness of peginterferon alfa and ribavirin in patients with chronic HCV who are:

- eligible for a shortened course of treatment compared with standard length of treatment
- eligible for re-treatment following previous non-response or relapse to treatment, compared with BSC
- co-infected with HIV, compared with BSC.

The economic analysis comprises:

- a systematic review of the literature on the cost-effectiveness of peginterferon and ribavirin treatment
- a review of studies of the HRQoL of patients with chronic HCV from the above patient groups
- a review of the drug manufacturers' submissions to NICE
- our independent economic model and cost-effectiveness evaluation (the SHTAC model).

Systematic review of existing cost-effectiveness evidence

A systematic review was undertaken to identify economic evaluations of peginterferon alfa and ribavirin in patients with chronic HCV in the subgroups outlined above (see *Chapter 3* for methods). The details of the search strategy are documented in *Appendix 2*.

Quantity and quality of the research available

A total of 142 references were identified by the search, of which one full paper and one conference abstract were retrieved for further inspection. The full paper was included, and the conference abstract was excluded. A second full paper was identified on searching the references of the included study, and this study met the inclusion criteria. Therefore, two full economic evaluations[64,65] met the inclusion criteria for the review. The study characteristics are presented in *Table 9*.

The two included studies evaluated treatment of HCV/HIV co-infected cohorts. No economic evaluations were identified in re-treated cohorts, or in patients who were eligible for shortened courses of treatment. Both included studies were conducted in the USA, and each of the studies compared peginterferon alfa and ribavirin with peginterferon alfa monotherapy, combined non-peginterferon alfa and ribavirin, and no treatment. An additional interferon alfa monotherapy arm was included in the Kuehne and colleagues study.[64] Kuehne and colleagues[64] present a cost–utility analysis, while in the more recent Campos and colleagues paper[65] a cost-effectiveness analysis is reported.

The included studies were assessed based on a checklist suggested for the critical appraisal of cost-effectiveness analysis by Drummond and colleagues,[67] the requirements of NICE for submissions on cost-effectiveness (reference case)[68] and a suggested guideline for good practice in decision modelling by Philips and colleagues.[69]

TABLE 9 Study characteristics of the included economic evaluations

	Kuehne and colleagues 2002[64]	Campos and colleagues 2007[65]
Publication year	2002	2007
Country	USA	USA
Study type	CUA model	CEA model
Study population	A cohort of HCV/HIV co-infected individuals	A treatment-eligible urban cohort, co-infected with HCV/HIV
Interventions	1. IFN α (48 weeks) 2. IFN α and RBV (24 and 48 weeks) 3. PEG α (48 weeks) 4. PEG α and RBV (48 weeks) 5. No treatment	1. PEG α-2a and RBV (48 weeks) 2. IFN α-2a and RBV (48 weeks) 3. PEG α-2a (48 weeks) 4. No treatment
Treatment effect modelled	Patients were assumed to have: 1. No treatment response: received no clinical benefit and were subject to their annual pretreatment risk of HCV-related liver disease progression 2. Partial but non-sustained response: did not progress in their HCV-related liver disease during treatment but were subject to pretreatment risks of liver disease once treatment was stopped 3. Patients with a sustained response (i.e. undetectable HCV RNA for >6 months after treatment) did not experience a future risk of HCV-related liver disease	SVR (in combination PEG α-2a and RBV) of 40%, based on one trial[66]
Currency base	US$	2004, US$

CEA, cost-effectiveness analysis; CUA, cost–utility analysis; IFN α, interferon alfa; PEG α, peginterferon alfa; RBV, ribavirin.

Judgements of the methodological quality of the included studies are shown in *Table 10*. Overall, the methodological quality of the two papers was judged to be variable.

Neither of the included studies derived the treatment effectiveness measure used in the evaluation from a systematic review. Kuehne and colleagues[64] cite several sources for the treatment efficacy measure. The study by Kuehne and colleagues[64] was conducted prior to the publication of trials of antiviral treatment in co-infected patients. The treatment efficacy measure therefore comes from studies of the treatment of mono-infected patients, and should therefore be viewed with caution. No details are reported on how, or if, these results have been statistically pooled. Campos and colleagues[65] used an effectiveness measure from a large RCT of co-infected patients: APRICOT (AIDS Pegasys Ribavirin International Co-infection Trial).[66] The use of the efficacy measure from this trial has not been justified within the paper.

Both of the included studies provide a clear statement of the decision problem, which is to assess the cost-effectiveness of the various interventions for HCV in a co-infected cohort, and adopt an appropriate model structure in order to address this.

Both models have been validated by comparing the predicted rate of future cirrhosis progression with those found in published cohort studies. Kuehne and colleagues[64] found a comparable rate of cirrhosis progression when comparing the model's predictions with a published cross-sectional study[70] (16.9% vs 14.9%, respectively). Campos and colleagues' model[65] was compared with a study of co-infected former injection drug-using patients by Di Martino and colleagues.[71] The rates were similar: 17.5% in the Di Martino and colleagues study[71] versus 16% in Campos and colleagues,[65] over the same follow-up period.

TABLE 10 Methodological quality of the included economic evaluations

	Kuehne and colleagues 2002[64]	Campos and colleagues 2007[65]
Is there a clear statement of the decision problem?	Yes	Yes
Is the perspective of the model clearly stated?	Unclear	Yes
Is the model structure appropriate and does it fit with the clinical theory of the disease process?	Yes	Yes
Are assumptions reasonable and appropriate?	Yes	Yes
Is the comparator routinely used in the UK NHS?	Yes	Yes
Is the study type and modelling methodology reasonable?	Yes	Yes
Is the patient group in the study similar to those of interest in the UK NHS?	Yes	Yes
Is the health-care system or setting comparable to the UK?	No	No
Have the costs and outcomes been discounted?	NR	Yes
Are the health states and parameters used in the model described clearly?	No	Unclear
Is the effectiveness of the intervention established based on a systematic review?	No	No
Are health benefits measured in QALYs using a standardised and validated generic instrument?	Unclear	No
Are the resource costs reasonable?	Unclear	Unclear
Has uncertainty been assessed?	Yes	Yes
Has the model been validated?	Yes	Yes

NR, not reported.

Kuehne and colleagues[64] stated that a societal perspective had been adopted, but with no indication of patient-borne costs. Costs and outcomes are discounted in the Campos and colleagues study[65] at 3%; no discount rate is reported in the Kuehne and colleagues paper.[64] Campos and colleagues[65] also clearly describe the perspective of the model as societal, with patient time costs being excluded.

The initial assumptions in both studies appear reasonable and appropriate, although several of the assumptions listed by Kuehne and colleagues[64] did not have any sources attached. While the assumptions adopted in both papers are broadly similar, the fibrosis rate in the absence of effective treatment was conditional on age and sex, and patients with decompensated cirrhosis were eligible for liver transplantation in the Campos and colleagues paper.[65] Kuehne and colleagues[64] assumed that minor adverse effects of treatment resulted in additional costs and a temporary decrease in QoL, and that major toxicity would result in discontinuation of treatment. This disutility is not defined in the paper, although the authors state that data from several studies are used to derive a 'plausible range' for the risk.

The health states used in the Campos and colleagues model[65] are described clearly, and appear relevant to the UK. The cost parameters and disease progression transition probabilities are reported, but how these are derived is unclear. The authors stated that they have been modified from previously published data, but did not elaborate further on the methods used, with the exception of the assumption that the rate of progression to decompensated cirrhosis was comparable between co-infected and mono-infected patients.

It is unclear whether the disease progression rates in the study by Kuehne and colleagues[64] have been derived from the literature or are empirically calibrated to the observed data. The relative risks (RRs) used in the base-case analysis for progression of cirrhosis in co-infected patients compared with mono-infected patients are not justified in the paper, although these are tested in

the sensitivity analysis. The liver disease utility values are sourced from several references, but, again, the methods used in pooling these results are not reported, and there is no explanation of how rates for co-infected patients have been derived from those of mono-infected patients.

The probabilities of SVR in the groups according to genotype and treatment in the two included studies are presented in *Table 11*.

Kuehne and colleagues' annual SVR probabilities[64] are considerably higher than those reported by Campos and colleagues[65] for interferon alfa and ribavirin for 48 weeks' duration [33% (28%–40%) vs 7%, respectively, in genotype 1]. This gap is more pronounced in the same treatment strategy for patients with genotype non-1: Kuehne and colleagues[64] reported 75% (61%–85%) compared with Campos and colleagues[65] reporting 18% for this group. The SVR probabilities are similar between the studies for peginterferon monotherapy and genotype 1: both studies reported 14% for genotype 1 and 46% by Kuehne and colleagues[64] versus 31% by Campos and colleagues[65] for genotype non-1. In patients receiving peginterferon combined with ribavirin these probabilities were again higher in the Kuehne study: [64] in genotype 1, Kuehne and colleagues[64] reported 42% (34%–45%) versus 29% in the Campos study,[65] and in genotype non-1 they were 79% versus 58% respectively. In all treatment strategies and genotypes, with the exception of genotype 1 and peginterferon alfa monotherapy, Kuehne and colleagues[64] employed higher probabilities of SVR, with the difference in the case of interferon alfa and ribavirin for 48 weeks being substantial. As mentioned earlier, these SVRs were based on mono-infected patients.

Health benefits in the Kuehne and colleagues study[64] are measured in years of life saved (YLS), in quality-adjusted life-months and QALYs. The authors stated that the quality weights for HCV-specific health states were derived from published studies using the visual analogue scale, and that HIV health states were derived from studies based upon the HIV Cost and Services Utilization Study.[72–75] It is not reported what instrument was used in this study. Campos and colleagues[65] measured health benefits in YLS.

Whether the selected resource costs are reasonable is judged to be unclear in both of the included studies. In both cases the costs are relevant to the US health-care system. Both studies used cost-of-care estimates from a study published in 1997,[76] which, in turn, modelled the cost-effectiveness of interferon alfa-2b, and in which the resources were based on estimates by a panel of hepatologists. A base year for costs is not given, but the authors state that all costs were converted to constant dollars. Hepatitis C costs were previously published costs, again based upon estimates from an expert panel. The costs of HIV care were based upon previously published studies; the authors stated that the estimates derived were similar to those given in other sources of costs incurred by HIV/AIDS.

Uncertainty is assessed in both of the included studies through sensitivity analyses. Univariate and multivariate sensitivity analyses were carried out in both studies to compare the effect of alternative assumptions compared with those in the base case. Selected results are reported. Neither study has reported a probabilistic sensitivity analysis (PSA) or cost-effectiveness acceptability curve (CEAC).

Relevance of the studies to the UK

The patient group in the model is similar to one of those currently of interest in this appraisal – patients co-infected with HIV. However, the Kuehne and colleagues study[64] focuses on patients with moderate HCV liver-related disease, whereas the current NICE guidance covers patients with moderate to severe[38] and mild chronic HCV.[33] The US health system, in which both of the studies are based, is not comparable to the UK NHS, and this will therefore extend to the costs incurred within it.

TABLE 11 Sustained virological response probabilities in the two included economic evaluations[64,65]

	Base-case probabilities (%)	
Treatment strategy	Kuehne and colleagues 2002[64]	Campos and colleagues 2007[65]
Interferon alfa (48 weeks)		
Genotype 1	6 (2–8)	
Genotype non-1	27 (15–28)	Not applicable
Interferon alfa + ribavirin (24 weeks)		
Genotype 1	16 (14–28)	Not applicable
Genotype non-1	69 (62–73)	
Interferon alfa + ribavirin (48 weeks)		
Genotype 1	33 (28–40)	7
Genotype non-1	75 (61–85)	18
Peginterferon alfa (48 weeks)		
Genotype 1	14 (12–31)	14
Genotype non-1	46 (40–67)	31
Peginterferon alfa + ribavirin (48 weeks)		
Genotype 1	42 (34–45)	29
Genotype non-1	79 (76–88)	58

Assessment of cost-effectiveness

The base-case results reported by Kuehne and colleagues[64] are presented in *Tables 12* and *13*, below, with a summary of those reported by Campos and colleagues[65] presented in *Table 14*. It is difficult to directly compare the results of the two studies, as they are reported very differently. Campos and colleagues[65] have reported their results by sex and genotype, whereas Kuehne and colleagues[64] have reported results by CD4 cell count (350 and 200 cells/μl), by mild or moderate disease, and by genotype 1 or genotype non-1. Both studies report the incremental cost by YLS, and Kuehne and colleagues[64] additionally present incremental costs per QALY for each subgroup.

In the Kuehne and colleagues study,[64] both peginterferon alfa monotherapy and peginterferon alfa plus ribavirin in combination dominated the other strategies in genotype 1 patients, with CD4 cell counts of 350 cells/μl and 200 cells/μl and mild chronic HCV, and in patients with a CD4 cell count of 200 cells/μl and moderate HCV. Peginterferon alfa monotherapy was the more cost-effective in each case. In patients with CD4 cell counts of 350 cells/μl and moderate HCV, peginterferon plus ribavirin and interferon plus ribavirin dominated, whereas the latter was the most cost-effective at US$11,600 versus US$40,000 for peginterferon in combination per QALY gained.

In the base-case analysis for genotype non-1 patients, again peginterferon alfa plus ribavirin in combination was not the most cost-effective of the treatment strategies tested. In patients in this group with mild disease, the monotherapies were dominated in each case. In patients with CD4 cell counts of 350 and 200 cells/μl, the lowest cost per QALY gained came from the 24-week course of interferon plus ribavirin at US$11,900 and US$104,400, respectively. In both cases, peginterferon and ribavirin (48 weeks) was the least cost-effective of the dominating strategies at US$300,800 in patients with 350 cells/μl, and US$4,000,000 in patients with 200 cells/l.

TABLE 12 Base-case results for genotype 1 co-infected patients (adapted from Kuehne and colleagues[64])

Patient group	Treatment type	US$/YLS	US$/QALY
Co-infected patients with CD4 cell counts of 350 cells/μl and mild chronic HCV	No treatment	–	–
	IFN 48 weeks	Dominated[a]	Dominated[a]
	IFN + RBV 24 weeks	Dominated[a]	Dominated[a]
	IFN + RBV 48 weeks	Dominated[b]	Dominated[b]
	PEG 48 weeks	107,900	35,900
	PEG + RBV 48 weeks	349,900	113,100
Co-infected patients with CD4 cell counts of 200 cells/μl and mild chronic HCV	No treatment	–	–
	IFN 48 weeks	Dominated[a]	Dominated[b]
	IFN + RBV 24 weeks	Dominated[a]	Dominated[a]
	IFN + RBV 48 weeks	Dominated[b]	Dominated[b]
	PEG 48 weeks	1,401,200	340,600
	PEG + RBV 48 weeks	4,293,900	937,200
Co-infected patients with CD4 cell counts of 350 cells/μl and moderate chronic HCV	No treatment	–	–
	IFN 48 weeks	Dominated[a]	Dominated[a]
	IFN + RBV 24 weeks	Dominated[a]	Dominated[a]
	IFN + RBV 48 weeks	18,500	11,600
	PEG 48 weeks	Dominated[b]	Dominated[b]
	PEG + RBV 48 weeks	65,100	40,000
Co-infected patients with CD4 cell counts of 200 cells/μl and moderate chronic HCV	No treatment	–	–
	IFN 48 weeks	Dominated[a]	Dominated[a]
	IFN + RBV 24 weeks	Dominated[a]	Dominated[a]
	IFN + RBV 48 weeks	Dominated[b]	Dominated[b]
	PEG 48 weeks	184,200	85,900
	PEG + RBV 48 weeks	594,800	267,200

IFN, non-peginterferon monotherapy; IFN + RBV, non-peginterferon and ribavirin combination therapy; PEG, peginterferon monotherapy; PEG + RBV, peginterferon and ribavirin combination therapy.

a This strategy is weakly dominated (i.e. eliminated by extended dominance) because it is less effective and is associated with a less attractive cost-effectiveness ratio than an available alternative strategy.

b This strategy is strongly dominated because it is more costly and less effective than an available alternative strategy.

In patients with genotype non-1 moderate HCV and a CD4 cell count of 350/μl, interferon monotherapy for 48 weeks was most cost-effective at US$2900 per QALY. Interferon in combination with ribavirin for 24 weeks was the most cost-effective strategy in patients with CD4 cell counts of 200 cells/μl and with moderate HCV.

Peginterferon alfa in combination with ribavirin dominated all other strategies (all assumed to have been received for 48 weeks) in each patient subgroup reported in the model by Campos and colleagues.[65] The authors' results suggested that the incremental cost per YLS of peginterferon with ribavirin in patients with genotype non-1 is approximately one-half of that of the incremental cost in patients with genotype 1. This is the case for both men and women.

In the Campos and colleagues study,[65] incremental costs per YLS saved were comparable between men and women with the same genotype of HCV virus: US$73,000 (men) versus US$70,000 (women) in genotype 1, and US$39,700 (men) versus US$39,300 (women) in genotype non-1. The incremental costs per YLS for each of the other strategies were not reported in detail, as they were dominated by peginterferon and ribavirin.[65]

TABLE 13 Base-case results for genotype non-1 co-infected patients (adapted from Kuehne and colleagues[64])

Patient group	Treatment type	US$/YLS	US$/QALY
Co-infected patients with CD4 cell counts of 350 cells/μl and mild chronic HCV	No treatment	–	–
	IFN 48 weeks	Dominated[a]	Dominated[a]
	IFN + RBV 24 weeks	37,400	11,900
	IFN + RBV 48 weeks	347,000	112,100
	PEG 48 weeks	Dominated[b]	Dominated[b]
	PEG + RBV 48 weeks	894,000	300,800
Co-infected patients with CD4 cell counts of 200 cells/μl and mild chronic HCV	No treatment	–	
	IFN 48 weeks	Dominated[a]	Dominated[a]
	IFN + RBV 24 weeks	541,300	104,400
	IFN + RBV 48 weeks	3,865,600	1,088,500
	PEG 48 weeks	Dominated[b]	Dominated[b]
	PEG + RBV 48 weeks	11,827,300	4,000,000
Co-infected patients with CD4 cell counts of 350 cells/μl and moderate chronic HCV	No treatment	–	–
	IFN 48 weeks	4700	2900
	IFN + RBV 24 weeks	Dominated[b]	Dominated[b]
	IFN + RBV 48 weeks	63,500	38,800
	PEG 48 weeks	Dominated[b]	Dominated[b]
	PEG + RBV 48 weeks	169,700	105,300
Co-infected patients with CD4 cell counts of 200 cells/μl and moderate chronic HCV	No treatment	–	–
	IFN 48 weeks	Dominated[a]	Dominated[a]
	IFN + RBV 24 weeks	67,900	29,800
	IFN + RBV 48 weeks	561,200	265,100
	PEG 48 weeks	Dominated[b]	Dominated[b]
	PEG + RBV 48 weeks	1,558,800	771,200

IFN, non-peginterferon monotherapy; IFN + RBV, non-peginterferon and ribavirin combination therapy; PEG, peginterferon monotherapy; PEG + RBV, peginterferon and ribavirin combination therapy.

a This strategy is weakly dominated (i.e. eliminated by extended dominance) because it is less effective and is associated with a less attractive cost-effectiveness ratio than an available alternative strategy.

b This strategy is strongly dominated because it is more costly and less effective than an available alternative strategy.

TABLE 14 Base-case results for genotype 1 and non-1 co-infected patients (reprinted from Campos and colleagues,[65] with permission from Elsevier)

Patient group	Treatment strategy	Incremental cost per YLS (US$)
Men		
Genotype 1	PEG + RBV	73,000
Genotype non-1	PEG + RBV	39,700
Women		
Genotype 1	PEG + RBV	70,000
Genotype non-1	PEG + RBV	39,300

PEG, peginterferon; RBV, ribavirin.

Interferon and ribavirin and peginterferon monotherapy were all included in the model as comparators but have been excluded here as these were dominated strategies. No treatment was also included as a comparator. This strategy assumed 48 weeks of HCV therapy for all patients.

Sensitivity analyses

The authors of both studies report that the results are sensitive to the discount rate. In Kuehne and colleagues,[64] this is a variable to which the results appear most sensitive; however, the discount rate applied in the base-case analysis was not reported. Campos and colleagues[65] describe their results as sensitive to the discount rate: a 0% rate resulted in an ICER 60% lower than the base case, whereas a 5% discount rate resulted in an ICER of 140% higher than the base case.

The results in both the included studies are sensitive to the fibrosis progression rates. In a two-way sensitivity analysis with the effectiveness of combination peginterferon alfa plus ribavirin and disease progression, Campos and colleagues[65] reported that cost-effectiveness ratios were < US$50,000 per YLS, regardless of fibrosis, when treatment efficacy exceeded 50%. This is higher than the base-case treatment efficacy of 40%. Where treatment efficacy was < 25%, cost-effectiveness ratios were < US$100,000 across the range of RRs, although these are described as having had 'slightly more influence' (p. 277).[65] No further details of how, or the degree to which, the RR is influential are reported. Kuehne and colleagues[64] reported that in mild HCV and peginterferon plus ribavirin the difference in their ICER from the base case was largest when the RR was between 1 and 2, with less sensitivity to RRs > 3. Changes in the RR of progression had a greater effect on the ICER in patients with mild HCV than in those with moderate HCV.

The order of the strategies described in the study by Campos and colleagues[65] remained the same when it was assumed that treatment was discontinued in the absence of an EVR – US$59,300 per YLS for men in genotype 1 versus US$33,100 per YLS for men in genotype non-1; the results in women again reflected this. The results were reported by the authors as being most sensitive to variation in the annual excess death rate owing to HIV, fibrosis progression rates and treatment efficacies in non-cirrhotic patients, and as being 'moderately' sensitive to drug costs. None of these was reported in detail across the patient subgroups or intervention strategies. Where no discount rate was applied this resulted in an ICER that was 60% lower than the base-case analysis; a 5% discount rate saw the ICER increase to 140% higher. The cost of the peginterferon alfa and ribavirin strategy was varied from 50% to 150% of the base-case value, which resulted in ICERs of between US$56,300 and US$88,000 per YLS, respectively. The variation in death rate owing to HIV was illustrated by an example of the excess mortality being reduced by 97%, reducing the ICER to US$41,000 per YLS. No justification for this reduction is described. However, where this was increased 11-fold to reflect death rates in patients with a history of severe opportunistic infections, treatment is dominated by non-treatment. No results are reported for the fibrosis progression rates or treatment efficacy one-way analyses.

Campos and colleagues[65] further describe a two-way sensitivity analysis whereby the effectiveness of the combination therapy of peginterferon alfa plus ribavirin and the RR of fibrosis progression due to co-infection were varied. Where efficacy was increased by 50%, the cost-effectiveness ratios decreased to < US$50,000 per YLS, and this was not sensitive to the variation in fibrosis progression. Where efficacy was decreased by 25% the cost-effectiveness ratios decreased to < US$100,000 per YLS. The authors state that this was 'slightly more' sensitive to fibrosis progression.

Kuehne and colleagues[64] performed a number of one-way sensitivity analyses in patients who were receiving interferon alfa plus ribavirin and peginterferon plus ribavirin. The ICERs were found to be most sensitive to the RR of progression to cirrhosis compared with mono-infected patients. In the figure in the study publication, the ICER appears most sensitive to the discount rate, HAART efficacy, relapse after a sustained response and cost of ribavirin in patients receiving interferon alfa combination therapy for 48 weeks compared with 24 weeks, as well as discount rate, relapse rate and HAART efficacy in peginterferon alfa plus ribavirin compared with

interferon alfa plus ribavirin for 48 weeks. Minor adverse events are reported as having little impact on the ICERs, while major toxicity in 20% of patients receiving 48 weeks of peginterferon combination therapy increased this ICER from US$40,000 to US$69,000. Decreasing utility estimates by 10% during 48 weeks of therapy led to this strategy dominating the non-peginterferon-based treatments.

The authors further reported that the ICER was minimally sensitive to minor toxic effects, with no further details. Major toxicity could affect the effectiveness of HAART in this group, and a sensitivity analysis was undertaken: if the effectiveness of HAART was reduced by 50% in 20% of the patients receiving peginterferon and ribavirin, the ICER increased from US$40,600 to US$69,000 per QALY.

Summary

- Two economic evaluations[64,65] of treatment strategies in patients co-infected with HCV/HIV were included in the review. No studies assessing the cost-effectiveness of shortened courses of treatment or re-treating patients who had not-responded to, or failed, previous therapy were identified.
- The papers were found to be of mixed methodological quality overall. The authors presented a clear decision problem in co-infected patients, using an appropriate study design and model structure. These were state-transition models with SVR as the main measure of treatment effectiveness. It is not clear how the effectiveness measures have been derived.
- The studies are both based in the USA and therefore both the setting and costs are unlikely to be generalisable to the UK NHS.
- There are notable differences in the SVR probabilities used by the two included studies. This is likely to be owing to SVRs in the study by Kuehne and colleagues[64] being derived from studies of mono-infected patients.
- The costs in both papers appear to have been taken from a previous published study in which resource use was estimated by expert opinion. The ICERs in the Campos and colleagues study[65] are sensitive to these costs.
- Sensitivity analyses have been reported in both studies, but a PSA has not been conducted in the Campos and colleagues paper,[65] where this would now be considered standard practice.
- Kuehne and colleagues[64] reported that their results in HCV/HIV co-infected patients were most sensitive to the RR of progression to cirrhosis compared with HCV mono-infected patients. It is difficult to ascertain from the paper how these RRs were derived.
- In the Kuehne and colleagues study,[64] a clear pattern does not emerge over the reported subgroups. While peginterferon plus ribavirin is a dominant strategy in each subgroup, it is not the most cost-effective strategy in any of these groups.
- Campos and colleagues[65] concluded that peginterferon alfa plus ribavirin is the dominating strategy in all patient subgroups reported. In contrast, Kuehne and colleagues[64] reported varied results across their subgroups, but in each, peginterferon and ribavirin combination therapy was the least cost-effective of the dominating strategies.
- These results should be viewed with caution owing to the mixed methodological quality of the included studies.

Review of manufacturers' submissions

Roche submission to NICE: cost-effectiveness analysis

Overview

The Roche submission to NICE in support of peginterferon alfa-2a consists of a 226-page written document (containing submitted evidence on the clinical effectiveness and a cost-effectiveness analysis) and a fully executable, electronic copy of the manufacturer's economic model. The MS

reports cost-effectiveness results for the three populations covered by the scope for this NICE appraisal:

- Patients who have previously been treated with peginterferon alfa, including both those who did not respond to previous treatment (by viral genotype) and those who relapsed on previous treatment. Costs and outcomes for these patients are compared with supportive care, in line with the scope for this appraisal.
- Patients with LVL and RVR who receive shortened courses of treatment with peginterferon alfa (by viral genotype). Costs and outcomes for these patients are compared with treatment for the same group of patients receiving the standard duration of treatment, in line with the scope for this appraisal.
- Patients co-infected with HCV/HIV. Costs and outcomes for these patients are compared with treatment for the same group of patients receiving non-peginterferon alfa therapy, which is not consistent with the scope for this appraisal.

The perspective of the analysis is not stated, but appears to be consistent with the NICE reference case[68] of the NHS and Personal Social Services (PSS), capturing direct costs and benefits only. The submission reports lifetime costs and outcomes (reported as life expectancy and QALYs) for each treatment arm and the incremental costs and outcomes for peginterferon alfa-2a combined with ribavirin compared with usual care (which varies between patient populations, as stated above).

Below we outline the approach taken by the manufacturer and provide an outline review based on a checklist suggested for the critical appraisal of cost-effectiveness analysis by Drummond and colleagues,[67] the requirements of NICE for submissions on cost-effectiveness (reference case),[68] and a suggested guideline for good practice in decision modelling by Philips and colleagues.[69]

Modelling approach

The cost-effectiveness analysis model adopted for the MS is a state-transition model that is structurally similar to published models previously used in the population of patients with chronic HCV,[76–81] including our previous assessment report[17] for NICE (TA106). The model has a lifetime horizon (in the base-case analysis the cohort simulation is truncated at patient age of 99 years), with a cycle length of 1 year, and is used to estimate the morbidity and cost resulting from progressive liver disease and treatment costs (up to a maximum duration of treatment with peginterferon alfa-2a of 72 weeks). The model has five health states indicating progressive liver disease (HCV, compensated cirrhosis, decompensated cirrhosis, HCC and liver transplantation), one state representing a treatment response (SVR) and one absorbing state (death), although this last state is broken down to differentiate deaths from progressive liver disease and deaths from all other causes. Unlike the model adopted in our previous assessment,[17] the model developed for the MS does not distinguish the stage of liver disease in non-cirrhotic patients with chronic HCV (i.e. there is no distinction between mild and moderate HCV). The impact of this structural assumption is not discussed in the MS.

The main treatment effect applied in the model is the SVR for treated patients, with the proportion of patients in each of the modelled populations achieving an SVR based on data from clinical trials conducted in the relevant patient populations, reported in the MS (discussed in *Data inputs*; see also *Appendix 3*). Patients who achieve an SVR are assumed in the model to be 'cured' and do not face any risk of reactivation of disease or any excess risk of progressive liver disease (above that of a general population). Age-specific mortality risks for the general population, weighted for the proportion of men in the baseline cohort, are applied to patients achieving an SVR. Patients who do not achieve an SVR are at risk of progressive liver disease and are assumed to face the same risks of disease progression as untreated patients. Risks of disease

progression and, where relevant, excess mortality risks associated with advanced liver disease states in the model have been drawn from natural history studies.

The base-case population in each analysis is the same, with all patients entering the model being non-cirrhotic, with chronic HCV. The simulated patient cohort has a mean age of 45 years, with 70% being male. These assumptions have no impact on response to treatment (i.e. SVRs in the model are not broken down by age or sex), but affect the all-cause mortality rates applied in the model. Patient weight is assumed to be greater than 75 kg – again this has no impact on the patient response to treatment, but has an impact on the cost of treatment, as ribavirin dosage is weight related. The MS discusses these assumptions in relation to the characteristics of patients recruited to the clinical trials used to estimate the SVRs applied in the model. However, there is no discussion of the relevance of these characteristics to the population of UK patients with chronic HCV or in the modelled populations.

Health-state utilities applied to the chronic HCV and progressive liver disease states in the model were taken from the UK Mild Hepatitis C Trial.[82] Age-specific utility values [reported for a general population survey using the European Quality of Life-5 Dimensions (EQ-5D[83]) and valued using a UK general population tariff[84]] were applied for only the SVR state. The MS does not discuss the possible implications of using age-specific utility values for one state and not for others (discussed in *Data inputs*). The model does not include treatment-related adverse events, other than to reduce utility in the year of treatment by 0.11 (from 0.66 to 0.55).

The costs applied in the submission were made up of two components. Treatment-related costs (which for peginterferon alfa-2a combination therapy consist of drug acquisition costs, monitoring of patients on treatment and surveillance of patients once treatment has stopped) were estimated separately from health-state costs. The latter relate to service use associated with management of progressive liver disease, associated with chronic HCV infection in patients who do not respond to treatment and for patients whose disease progresses despite demonstrating a response to treatment.

Drug usage for peginterferon alfa-2a was based on a dosage of 180 µg/week, supplied in a prefilled syringe and self-administered by patients, at a cost of £126.91. The dose of ribavirin used in combination with peginterferon alfa-2a varies by patient group and by weight, in the case of genotype 1 patients (*Table 15*). Expected duration of treatment with the combination of peginterferon alfa-2a plus ribavirin also varies by patient group (see *Table 15* for a summary).

Resource use for patient monitoring associated with peginterferon alfa-2a and ribavirin combination therapy and surveillance of patients following treatment cessation was estimated using management protocols, which were developed using expert opinion for our previous report[17] for NICE (TA106). The original costing protocols were slightly modified (to include quantitative, rather than qualitative, HCV viral load at key assessment stages) and were inflated to 2007–8 prices using the Hospital and Community Health Services (HCHS) Pay and Prices Index[85] (*Table 16*).

Health-state costs in the model are based on values adopted in our previous assessment,[17] inflated from 2003–4 to 2007–8 prices using the HCHS Pay and Prices Index[85] (*Table 17*).

Model/cost-effectiveness results

The MS reports total costs (broken down as treatment-related costs and future costs of medical care for HCV) and outcomes (life expectancy and QALYs) for peginterferon alfa-2a combination therapy and each comparator modelled separately, as well as an incremental analysis (these are summarised in *Table 18*). Scatter plots showing the cost-effectiveness plane (incremental cost and

TABLE 15 Drug acquisition costs in the Roche model

Patient group included in model	RBV dose per day (mg)	RBV cost per week (£)	Treatment duration (weeks)
Re-treatment of non-responding patients			
Genotype 1	1000/1200[a]	84.15/100.98	72
Genotype non-1	800	67.32	48
Re-treatment of relapsed patients			
Genotype 1	1000/1200[a]	84.15/100.98	48
Genotype non-1	800	67.32	48
Shortened duration of treatment			
Genotype 1	1000/1200[a]	84.15/100.98	48/24[b]
Genotype 2/3	800	67.32	24/16[b]
HCV/HIV co-infected			
All genotypes	800	67.32	48

RBV, ribavirin.
a Weight-based RBV dosage for genotype 1 patients – 1000 mg per day for body weight < 75 kg and 1200 mg per day for body weight ≥ 75 kg.
b Shortened duration of treatment – first value is standard duration, second number is shortened duration. Dosing is constant across duration of treatment.

TABLE 16 On-treatment monitoring and post-treatment monitoring for patients receiving peginterferon alfa-2a combination therapy, by duration of treatment

Duration of treatment	Cost (£)
On-treatment monitoring (weeks)	
12 weeks	568
16 weeks	600
24 weeks	795
48 weeks	1473
72 weeks	1711
Post-treatment surveillance	
Non-responders	102
Responders (SVR)	167

TABLE 17 Health-state costs applied in the Roche model

Health state	Health-state cost (£)
Moderate chronic hepatitis C	843
CC	1338
DC	10,725
HCC	9557
Liver transplantation, first year	43,263
Liver transplantation, subsequent years	1628

CC, compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma.

TABLE 18 Base-case results from Roche cost-effectiveness analysis

Patient group	Genotype	Treatment	Cost (£)	QALYs	ICER (£ per QALY gained)
Non-responders	1	No treatment	27,114	11.06	3334
		PEG α-2a + RBV[a]	29,224	11.69	
	Non-1	No treatment	27,114	11.06	809
		PEG α-2a + RBV[b]	27,942	12.08	
Relapsed on previous treatment	All	No treatment	27,114	11.06	Dominant
		PEG α-2a + RBV	21,199	13.74	
Shortened treatment duration for patients with LVL and RVR	1 + 4	PEG α-2a + RBV 48 weeks	13,387	15.78	15,472
		PEG α-2a + RBV 24 weeks	8866	15.49	
	2 + 3	PEG α-2a + RBV 24 weeks	8053	15.64	2719
		PEG α-2a + RBV 16 weeks	7391	15.39	
HCV/HIV co-infected patients	All	IFN α-2a + RBV	32,431	11.62	Dominant
		PEG α-2a + RBV	28,786	12.99	

PEG α, peginterferon alfa; RBV, ribavirin.
a Seventy-two weeks' treatment for patients showing an EVR, 12 weeks' treatment for patients not showing an EVR.
b Forty-eight weeks' treatment for patients showing an EVR, 12 weeks' treatment for patients not showing an EVR.

incremental QALYs for peginterferon alfa-2a combination therapy) from PSA are also reported for each patient population, as well as CEACs for re-treatment of patients who failed to respond to previous treatment with peginterferon.

The MS states that peginterferon alfa-2a in combination with ribavirin is cost-effective in all modelled comparisons for all populations (below a threshold of £15,000), emphasising that treatment dominates the 'current standard of care' for relapsed patients and for those with HCV/HIV co-infection. These conclusions are reflected in the manufacturer's PSA where:

- the probability of peginterferon alfa-2a combination being cost-effective (at a threshold of £20,000) was 100% for re-treating patients who failed to respond to previous peginterferon treatment (both for genotype 1 and genotype non-1 patient subgroups)
- treatment for patients who relapsed on previous peginterferon alfa treatment and for HCV/HIV co-infected patients was dominated in the majority (99%) of simulations. However, as stated earlier, the comparator included in the model for HCV/HIV co-infected patients was non-peginterferon alfa combination therapy – not supportive care as specified in the scope.

The interpretation of the results of the model for patients receiving shortened duration of treatment is complicated by the fact that, although shortened treatment duration is associated with significant savings in treatment costs, it incurs a penalty in terms of a reduced SVR compared with standard durations (from 97% to 91% for genotypes 1 and 4 and from 94% to 89% for genotypes 2/3). As a result, the incremental cost and incremental QALYs associated with shortened treatment duration are negative (for genotypes 1 and 4 the total cost is reduced by £4500 and total QALYs are 0.29 lower, whereas for genotypes 2 and 3 the total cost is reduced by £660 and total QALYs are 0.25 lower), yielding a positive ICER. However, this cannot be interpreted using the commonly assumed decision rule – is the ICER below a given (arbitrary) threshold – as the manufacturer's have done in their conclusions (section 7.5, p. 182 of the MS), selecting a threshold of £15,000 per QALY gained. In this situation the logic is reversed whereby ICERs *below* the threshold are *rejected*.[86] This can perhaps be better understood by considering the analysis using the net benefits framework where we would accept an intervention with positive incremental net benefit, i.e. where the value of incremental benefits exceeds the

incremental costs (see *Appendix 8* for more details). This requires costs and benefits to be valued on the same scale – commonly achieved by multiplying the incremental effect (incremental QALYs) by a given threshold value (willingness to pay per QALY gained), as below:

$$\text{Incremental net (monetary) benefit} = \lambda \times \Delta E - \Delta C$$

where ΔE is incremental QALYs, ΔC is incremental cost and λ is the threshold.

Applying this framework to the analysis of patients receiving shortened duration of treatment presented by the manufacturer, for a range of threshold values (λ) from £0 to £30,000 per QALY gained (*Table 19*), the incremental net monetary benefit for shortened duration of treatment is positive for genotype 2/3 at only comparatively low threshold values (below the ICER value of £2719). For genotype 1/4 patients the incremental net monetary benefit is positive over a wider range of willingness-to-pay values (below the ICER value of £15,472).

Outline appraisal of the cost-effectiveness analysis undertaken

The NICE reference case requirements (Roche) are shown in *Table 20*.

Outline review of modelling approach

Model structure/structural assumptions

The MS reports that update searches of MEDLINE and EMBASE (based on the search strategies from our previous assessment[17]) were conducted to identify economic evaluations published since the searches reported in our previous assessment.[17] This search is not discussed in the

TABLE 19 Incremental net monetary benefits for shortened treatment duration from manufacturer's analysis

	ΔC	ΔE	0	£10,000	£20,000	£30,000
Genotypes 1 + 4	–£4521	–0.29	4521	1599	–1323	–4245
Genotypes 2 + 3	–£662	–0.24	662	–1773	–4208	–6643

TABLE 20 National Institute for Health and Clinical Excellence reference case requirements (Roche)

NICE reference case requirements[68]	Included in submission
Decision problem: as per the scope developed by NICE	×[a]
Comparator: alternative therapies routinely used in the UK NHS	✓
Perspective on costs: NHS and PSS	✓
Perspective on outcomes: all health effects on individuals	✓
Type of economic evaluation: cost-effectiveness analysis	✓
Synthesis of evidence on outcomes: based on a systematic review	×[b]
Measure of health benefits: QALYs	✓
Description of health states for QALY calculations: use of a standardised and validated generic instrument	✓
Method of preference elicitation for health-state values: choice-based method (e.g. TTO, SG, not rating scale)	✓
Source of preference data: representative sample of the public	✓[c]
Discount rate: 3.5% pa for costs and health effects	✓

pa, per annum; SG, standard gamble; TTO, time trade-off.

a Comparator for HCV/HIV co-infected patients is IFN α-2a + RBV, not supportive care 'without any form of interferon therapy', as stated in the NICE scope.

b See *Appendix 3*.

c Health-state utilities come from a combination of sources – UK Mild Hepatitis C Trial for HCV and progressive liver disease states, but population survey for SVR states (age specific). The use of age-specific utilities for SVR, without using age-specific values for chronic liver disease states, is likely to lead to an overestimation of the utility gain from treatment response.

main body of the submission, but is included in an appendix. The appendix to the MS states that the purpose of this review was to identify more recent sources (for transition probabilities, costs and utilities) to populate the economic model. The MS does not report full details on any of the economic evaluations identified by this search, nor whether any of these were conducted for patient populations covered by this review. The MS does not present a review of published economic evaluations or discuss alternative approaches to modelling the cost-effectiveness of antiviral treatment for chronic HCV infection.

The manufacturer's model is structurally similar to published models previously used in the population of patients with chronic HCV,[76–81] including our previous assessment.[17] The states representing more advanced liver disease in the model (compensated cirrhosis, decompensated cirrhosis, HCC and liver transplantation) are commonly accepted as distinct stages of progressive liver disease, which can be distinguished by their impact on QoL, resource use or excess mortality risk. However, this model does not distinguish the stage of disease in non-cirrhotic patients with chronic HCV. In terms of the health-state utility value (0.66) and the transition probability for progressing to compensated cirrhosis (0.037), this health state has the characteristics of moderate HCV. There is no discussion in the MS of the rationale for adopting this structure nor of the possible implications, for the cost-effectiveness analysis, of assuming that all patients enter the model with moderate HCV (as opposed to mild or severe HCV). The MS does not report any evidence of approaches to establish the internal consistency of the model, or any evidence of external validation (by expert clinical opinion or by comparison with other published economic evaluations).

The effect of treatment is to induce an SVR in a proportion of patients, which is assumed to be a permanent cure. This approach is in accordance with previously published models in this patient population and would agree with long-term follow-up studies of patients achieving SVR on treatment. However, recent publications have highlighted a risk of liver cancer in patients who have undergone SVR – particularly in patients with compensated cirrhosis at baseline – which, while lower than for non-responding patients, is not completely eradicated. A retrospective study of 920 Italian patients with cirrhosis treated with interferon reported HCC incidence rates of 0.66 per 100 person-years of follow-up (95% CI 0.27 to 1.37) for those who achieved an SVR, and 2.10 per 100 person-years of follow-up (95% CI 1.75 to 2.51) for non-SVR patients.[87] The hazard ratio for HCC in non-SVR patients compared with those who achieved an SVR was 2.59 (95% CI 1.13 to 5.97). The manufacturer's model assumes a zero risk of HCC for patients in the SVR state: this may be reasonable given that all patients were assumed to enter the model in the chronic HCV state. However, under current guidance, patients with compensated cirrhosis may undergo treatment with peginterferon alfa, and a model that allowed patients to enter in all treatment-eligible states would be likely to produce more generalisable results.

Treatment-related adverse events are not included in the model, other than to reduce utility in the year of treatment by 0.11 (from 0.66 to 0.55). The exclusion of the costs of adverse events from the model is justified in the MS on the basis that the most commonly occurring treatment-related adverse events are unlikely to be associated with substantial treatment costs, and that no specific subgroup of adverse events accounts for more than 2% of the populations in any of their included clinical trials. The exclusion of treatment costs for adverse events is in line with the approach adopted in previously published economic evaluations of antiviral treatment for chronic HCV.

Data inputs

The main treatment effect applied in the model is the SVR for treated patients. For patients who failed to respond or relapsed on previous peginterferon therapy, the SVRs for treated patients were taken from clinical trials (Jensen and colleagues[88] for non-responders and Berg and

colleagues[89] for patients who relapsed – see *Appendix 3*). The SVR for the no treatment group was assumed to be zero, as none of the trials was placebo controlled or contained BSC arms. As acknowledged in the MS, the SVR reported by Berg and colleagues[89] may be higher than would be expected in more generalisable populations of relapsed patients. Genotype 1 patients, who were subsequently enrolled in the study by Berg and colleagues,[89] had relapsed following initial treatment that was less intensive than would be regarded as the current standard of care for this patient group [they received 24 weeks, rather than 48 weeks, of peginterferon combination treatment with a lower dosage of ribavirin (800 mg) than is recommended].

For patients receiving shortened durations of treatment, the SVRs for both groups in the model were taken from unpublished subgroup analyses of clinical trial subjects. For genotype 2 and 3 patients the subgroups were taken from the trial reported by Shiffman and colleagues,[90] and for genotype 1 and 4 subgroups appear to have been taken from the trial reported by Hadziyannis and colleagues[91] (referred to as trial NV15942 in the submission; these data are reported in table 8 of the SPC for peginterferon alfa-2a[42]). For patients with HCV/HIV co-infection, the SVRs were taken from a clinical trial comparing non-peginterferon alfa-2a with peginterferon alfa-2a[66] – as stated earlier, this is not consistent with the scope for this appraisal.

The EVRs applied in the model for re-treated patients were taken from the same trials (Jensen and colleagues[88] for non-responders and Berg and colleagues[89] for patients who relapsed). These have the effect of reducing the cost of treatment by ceasing drug treatment in patients who do not show an EVR (in line with the SPC for peginterferon alfa-2a; see p. 4 of SPC [42]).

As discussed above, update searches for economic evaluations published since our previous assessment[17] are reported in an appendix to the MS, which states that the purpose of this review was to identify more recent sources (for transition probabilities, costs and utilities) to populate the economic model. It further states that '13 full publications were considered for further informing the economic evaluation in this submission' (p. 216), but gives only brief details (lead author and date of publication) for six publications (one of which is our previous assessment and a further three are referenced in our previous assessment). The transition probabilities for the natural history model appear to have been taken from our previous assessment.[17]

The MS reports that an update search (based on the search strategy from our previous assessment[17]) of MEDLINE, EMBASE, PREMEDLINE and EMBASE Alert was conducted to find newer health-state utility values than those used in our previous assessment.[17] This search is not discussed in the main body of the submission but is included in an appendix, which concludes that no new relevant utility data have been published. The manufacturer does not appear to have attempted targeted searches for QoL or utility data in the specific populations of patients included in its submission. As a result, the model uses utility values from the UK Mild Hepatitis C Trial,[82] for chronic HCV and advanced liver disease states. However, age-specific utilities values from a general population were applied for the SVR state, which may lead to an overestimation of the utility gain, for two reasons:

- The age-specific utility values are substantially higher than the utility values for the SVR state reported from the UK Mild Hepatitis C Trial.[82] The age-specific utility for a 45-year-old patient achieving an SVR in the manufacturer's model is 0.85, declining to 0.73 once the patient is aged >75 years. In contrast, the utility for patients achieving an SVR from moderate HCV, using the UK Mild Hepatitis C Trial[82] valuations, is 0.72. The equivalent value for patients achieving an SVR from mild HCV is 0.82.
- All patients enter the model with moderate HCV, which has a utility value of 0.66, whereas the value for mild HCV is 0.77.

The MS reports that no new sources for health-state costs were identified by their updated searches and that they have used the values from our previous assessment,[17] inflated from 2003–4 to 2007–8 prices using the HCHS Pay and Prices Index.[85]

Assessment of uncertainty

Uncertainty is addressed using deterministic sensitivity analysis (DSA) and PSA. The DSAs were limited in scope and focused on characteristics not included in the PSA, and might more accurately be termed 'scenario analyses', as they deal with alternative assumptions rather than variability in input parameters. These analyses address issues of methodological uncertainty (varying discount rates), parameter uncertainty (using alternative assumptions for baseline characteristics including patients' mean age and weight as well as the proportion of women in the baseline cohort) and structural uncertainty (duration of surveillance for patients following cessation of treatment). The MS reports the incremental cost and effect, as well as the ICER, for each of the sensitivity analyses to facilitate interpretation of changes in the ICER in relation to alternative assumptions. The ICERs were largely insensitive to changes assessed in the DSA and none of these analyses would lead to a change in conclusion from the base-case analysis. The greatest variation was associated with differences in the starting age for the cohort (where incremental cost tended to reduce and incremental effect tended to increase with younger starting ages) and discounting practice (where re-treatment of non-responding patients became dominant for discount rates of 0% for both costs and effects). Additional DSAs were conducted for the HCV/HIV co-infected cohort to consider alternative assumptions regarding the excess death rate for co-infected patients. In the analysis presented in the MS peginterferon alfa-2a, treatment was dominant for all scenarios; however, this was for the comparison with non-peginterferon alfa, rather than with BSC.

Parameter uncertainty is also addressed in a PSA. The majority of parameters in the model are included in the PSA, including transition probabilities in the natural history model, health-state utilities, health-state costs, on-treatment monitoring and post-treatment surveillance costs, as well as SVR and (where appropriate) EVR probabilities. The choice of distribution applied to model parameters appears appropriate, beta distributions for utilities and probabilities and log-normal distributions for costs. However, the parameterisation for many of the distributions does not make best use of the available data. The SVR and EVR probabilities have been parameterised using the point estimate from the base-case analysis as the mean of the distribution, as would be expected, with the standard error (SE) assumed to be 0.02 (the implications of this assumption are discussed below). The rationale for this assumption is not discussed in the MS. The MS presents (for each trial used to derive the base-case SVR and EVR for each modelled population) the total number of patients in each arm, and the number achieving SVR and, where relevant, EVR, but it is not clear why these observed values were not used to parameterise the distributions. Similarly, the SEs for health-state costs have been assumed at 20% of the mean value, without any justification for this assumption. Standard deviations and the number of observations for the health-state costs are reported by the UK Mild Hepatitis C Trial[82] and could have been used to parameterise the distributions. Scatter plots of incremental cost and incremental QALYs are presented for all comparisons, while CEACs are presented only for re-treatment of patients who failed to respond to previous peginterferon treatment. There is no discussion of this in the MS and the presentation of the PSA is generally inadequate in the context of current NICE methodological guidance.[68]

The key source of heterogeneity in the modelled populations, in terms of response to treatment, has been taken into account through the presentation of separate analyses for viral genotype – either characterised as genotype 1 and genotype non-1 in the case of re-treatment of patients who did not respond to prior peginterferon treatment, or as genotype 1/4 and genotype 2/3

for shortened treatment duration. The remaining analyses (re-treatment of patients who did not relapse following prior peginterferon treatment and HCV/HIV co-infected patients) were not stratified by genotype. The MS does not discuss how representative the overall SVR from included clinical trials (which will reflect the genotype distribution of patients in the trial population) is of the overall SVR expected in a UK population of patients with chronic HCV, which may have a different genotype distribution. The MS has not considered another important source of heterogeneity, in terms of response to treatment, which is the stage of disease at treatment. Where trials have analysed SVR by stage of disease they tend to indicate that response is lower in patients with cirrhosis.

Summary of general concerns

- The manufacturer's model appears likely to overestimate the QALY gain from achieving SVR by:
  - applying age-specific utilities to the SVR state and not applying age-specific utilities to other health states
  - collapsing the HCV state into one, rather than differentiating mild and moderate HCV (which appear to have different health-state values).
- The model assumes that all patients start treatment in the moderate HCV state. It is likely that some patients will present at other stages of liver disease, including compensated cirrhosis. The base-case results, applying to patients with moderate liver disease, may not apply to this group.
- The manufacturer's model does not include the cost of the health state patients are in when they start treatment.
- The cost applied for surveillance of patients who achieve an SVR is low compared with that estimated in the UK Mild Hepatitis C Trial. This cost is applied only for the year following transition to the SVR state.
- The manufacturer's model appears to be applying an incorrect cost for ribavirin (for genotype 2/3 patients and for the HCV/HIV co-infected group).
- The parameterisation of some distributions in the PSA is based on assumed values and could be improved on. Additionally, some logically related parameters appear to be sampled independently in the PSA, which is likely to give misleading results.

Additional analyses undertaken by SHTAC

The assessment group undertook additional analyses using the manufacturer's model to address some of the concerns raised in the previous section. *Table 21* reports the results of the additional analyses undertaken for the population of patients eligible for shortened duration of treatment. All of the changes made to the manufacturer's model have the effect of increasing the value of the ICER. However, it needs to be borne in mind when interpreting these results that the incremental costs and outcome when comparing shortened with standard treatment duration are negative. The majority of the changes in assumptions in the model reduce the incremental QALYs between standard treatment and shortened duration – the exception is the change in the distribution of patients across stages of disease (to assume 32% of the cohort have cirrhosis prior to starting treatment).

Table 22 reports the results of the additional analyses undertaken for the population of non-responding or relapsing patients undergoing re-treatment. For non-responding patients the ICER increases in value for each of the scenarios examined, with the results for both genotype groupings being most sensitive to changes in the distribution of patients across stages of disease at baseline. However, although these analyses suggest that the ICER for re-treating patients with peginterferon alfa-2a combination therapy may be higher than the manufacturer's base case, they do not substantially alter the conclusions from the analysis. In all of the alternative scenarios, re-treatment of relapsing patients remains dominant.

TABLE 21 Additional analysis for patients eligible for shortened duration of treatment with peginterferon alfa-2a combination therapy

		Genotypes 1 + 4		Genotypes 2 + 3	
		Cost (£)	Outcome	Cost (£)	Outcome
Original	Standard	13,387	15.78	8053	15.63
	Shortened	8866	15.49	7391	15.39
	ICER	*15,472*		*2719*	
Do not use age-specific utility	Standard	13,387	14.16	8053	14.07
	Shortened	8866	13.97	7391	13.91
	ICER	*23,541*		*4137*	
Stage distribution (50 : 50, mild/moderate)	Standard	13,125	15.83	7529	15.73
	Shortened	8081	15.64	6431	15.57
	ICER	*26,146*		*6830*	
Stage distribution (33 : 35 : 32, mild/moderate/CC)	Standard	13,358	15.78	7995	15.62
	Shortened	8780	15.47	7285	15.37
	ICER	*15,071*		*2805*	
Add cost of original health state to year 1 SVR	Standard	13,796	15.78	8449	15.63
	Shortened	8866	15.49	7391	15.39
	ICER	*16,872*		*4347*	
All together[a]	Standard	13,735	14.16	8360	14.05
	Shortened	8780	13.95	7285	13.88
	ICER	*24,334*		*6336*	

a Use constant health-state utility from UK Mild Hepatitis C Trial for SVR rather than age-specific norms, assume patients are distributed across all treatment-eligible stages prior to treatment (33% mild chronic HCV, 35% moderate chronic HCV and 32% cirrhotic) and add the cost of the original health state to costs of patients achieving SVR (for first cycle only).

TABLE 22 Additional analysis for non-responding patients and for relapsing patients treated with peginterferon alfa-2a combination therapy

		Non-responders				Relapsers	
		Genotype 1		Genotype non-1		All genotypes	
		Cost (£)	Outcome	Cost (£)	Outcome	Cost (£)	Outcome
Original	BSC	27,114	11.06	27,114	11.06	27,114	11.06
	PEG α-2a	29,225	11.69	27,942	12.08	21,199	13.74
	ICER	*3334*		*809*		*PEG dominates*	
Do not use age-specific utility	BSC	27,114	11.06	27,114	11.06	27,114	11.06
	PEG α-2a	29,225	11.47	27,942	11.73	21,199	12.82
	ICER	*5073*		*1232*		*PEG dominates*	
Stage distribution (50 : 50 mild and moderate)	BSC	18,392	12.71	18,392	12.71	18,392	12.71
	PEG α-2a	21,637	13.13	21,052	13.39	17,274	14.48
	ICER	7763		3939		PEG dominates	
Stage distribution (33 : 35 : 32 mild/moderate/CC)	BSC	26,153	10.86	26,153	10.86	26,153	10.86
	PEG α-2a	28,389	11.52	27,183	11.93	20,766	13.65
	ICER	*3397*		*968*		*PEG dominates*	
Add cost of original health state to year 1 SVR	BSC	27,114	11.06	27,114	11.06	27,114	11.06
	PEG α-2a	29,280	11.69	28,030	12.08	21,431	13.74
	ICER	*3421*		*896*		*PEG dominates*	

continued

TABLE 22 Additional analysis for non-responding patients and for relapsing patients treated with peginterferon alfa-2a combination therapy *(continued)*

		Non-responders				Relapsers	
		Genotype 1		Genotype non-1		All genotypes	
		Cost (£)	Outcome	Cost (£)	Outcome	Cost (£)	Outcome
All together[a]	BSC	26,153	10.86	26,153	10.86	26,153	10.86
	PEG α-2a	28,440	11.31	27,265	11.58	20,980	12.73
	ICER	*5182*		*1559*		*PEG dominates*	

PEG α, peginterferon alfa.

a Use constant health-state utility from UK Mild Hepatitis C trial for SVR rather than age-specific norms, assume patients are distributed across all treatment-eligible stages prior to treatment (33% mild chronic HCV, 35% moderate chronic HCV and 32% cirrhotic) and add the cost of the original health state to costs of patients achieving SVR (for first cycle only).

TABLE 23 Additional analysis for HCV/HIV co-infected patients undergoing treatment with peginterferon alfa-2a combination therapy

		Cost (£)	Outcome
Original	BSC	27,022	11.03
	PEG α-2a	28,786	12.99
	IFN α-2a	32,431	11.62
	ICER	*903*	
Do not use age-specific utility	BSC	27,022	11.03
	PEG α-2a	28,786	12.32
	IFN α-2a	32,431	11.42
	ICER	*1372*	
Stage distribution (50 : 50, mild/moderate)	BSC	18,320	12.68
	PEG α-2a	23,565	13.97
	IFN α-2a	24,773	13.07
	ICER	*4050*	
Stage distribution (33 : 35 : 32, mild/moderate/CC)	BSC	26,080	10.84
	PEG α-2a	28,221	12.87
	IFN α-2a	31,602	11.45
	ICER	*1054*	
Add cost of original health state to year 1 SVR	BSC	27,022	11.03
	PEG α-2a	28,955	12.99
	IFN α-2a	32,431	11.62
	ICER	*989*	
All together	BSC	26,080	10.84
	PEG α-2a	28,377	12.20
	IFN α-2a	31,602	11.25
	ICER	*1684*	

IFN α, interferon alfa; PEG α, peginterferon alfa.
The base case presented in the MS compared PEG α-2a with IFN α-2a. The ICERs reported in this table are for PEG α-2a compared with BSC. IFN α-2a is included in the table for comparability with original results in the MS.

Table 23 reports the results of the additional analyses undertaken for the population of HCV/HIV co-infected patients. The results are similar to those for other patient groups – the ICER increases in value for each of the scenarios examined, with the results for both genotype groupings being most sensitive to changes in the distribution of patients across stages of disease at baseline. As

before, while these analyses suggest that the ICER for treating HCV/HIV co-infected patients with peginterferon alfa-2a combination therapy may be higher than the manufacturer's base case, they do not substantially alter the conclusions from the analysis.

Schering-Plough submission to NICE: cost-effectiveness analysis

Overview

The Schering-Plough submission[92] to NICE consists of a 69-page written document (containing submitted evidence on the clinical effectiveness and a cost-effectiveness analysis) and a fully executable, electronic copy of the manufacturer's economic model. The MS reports cost-effectiveness results for two populations covered by the scope of the NICE appraisal:

- Patients who have been treated previously with peginterferon, and who did not respond to previous treatment or who relapsed on previous treatment. This analysis is reported for all patients (a cohort including patients of all viral genotypes) and broken down by broad genotype categories (genotypes 1 and 4 combined or genotypes 2 and 3 combined). Costs and outcomes for these patients is compared with BSC, in line with the scope for this appraisal.
- Patients co-infected with HCV/HIV. This analysis is reported for all patients (a cohort including patients of all viral genotypes) and broken down by broad genotype categories (genotypes 1 and 4 combined or genotypes 2 and 3 combined). Costs and outcomes for these patients are compared with BSC, in line with the scope for this appraisal.

No assessment is presented on the cost-effectiveness of shortened versus standard treatment duration. The reason for this omission is not discussed by the manufacturer, though it may be due to peginterferon alfa-2b being licensed only for shorter treatment durations in genotype 1 (as opposed to genotypes 2, 3 and 4).

The perspective of the analysis is stated as being that of the NHS and PSS, consistent with the NICE reference case.[68] The submission reports lifetime costs and outcomes (reported as QALYs) for each treatment arm and the incremental costs and outcomes for peginterferon alfa-2b combined with ribavirin compared with BSC.

The MS does not report whether a systematic search was undertaken for economic evaluations of peginterferon alfa-2b or other treatments for chronic HCV in the patient populations covered by the scope, nor does it report any detail on the development and validation (including any details of clinical validation) of the model adopted for the MS.

Below we describe the approach taken for the model and provide an outline review based on a checklist suggested for the critical appraisal of cost-effectiveness analysis by Drummond and colleagues,[67] the requirements of NICE for submissions on cost-effectiveness (reference case)[68] and a suggested guideline for good practice in decision modelling by Philips and colleagues.[69]

Modelling approach

The model consists of an initial decision tree covering the first year in the model, where patients are eligible to receive treatment. The decision tree incorporates two chance nodes: the first of these applies a probability of patients achieving an EVR, the second applies a probability of patients who achieved an EVR (and therefore remained on treatment) achieving an SVR. A state-transition model is then used to model patients' costs and outcomes, depending on the state in which they emerge from the decision – with an SVR, remaining with HCV/compensated cirrhosis, or dead from all causes. The state-transition model is structurally similar to published models previously used in the population of patients with HCV, including the previous assessment report for NICE.[17] The model has six health states (mild HCV, moderate HCV, compensated cirrhosis, decompensated cirrhosis, HCC and liver transplantation) indicating

progressive liver disease, one state representing a treatment response (SVR) and one absorbing state (death), although this last state is broken down to differentiate deaths from progressive liver disease and deaths from all other causes.

The model does not differentiate the SVR state according to patients' stage of disease prior to SVR. However, QoL data reported by the UK Mild Hepatitis C Trial[82] would suggest that there are differences in health-state utility for patients who enter the SVR state from both mild and moderate chronic HCV, and it may be more appropriate to structure the model to identify prior stage of disease (given that patients with compensated cirrhosis are eligible to receive treatment, as well as those with mild or moderate chronic HCV).

The main treatment effect applied in the model is the SVR for treated patients, with the proportion of patients in each of the modelled populations achieving an SVR being based on data from clinical trials conducted in the relevant patient populations, reported in the MS. Patients who achieve an SVR are assumed in the model to be 'cured' and do not face any risk of reactivation of disease or any excess risk of progressive liver disease (above that of a general population). Age-specific mortality risks for the general population, weighted for the proportion of men in the baseline cohort, are applied to patients achieving an SVR. Patients who do not achieve an SVR are at risk of progressive liver disease and are assumed to face the same risks of disease progression as untreated patients. Risks of disease progression and, where relevant, excess mortality risks associated with advanced liver disease states in the model have been drawn from natural history studies.

The base-case population characteristics (in terms of age at entry to the model, weight and the proportion that are male) differ between the patient subgroups modelled and are based on the baseline populations in the relevant clinical trials. These assumptions have no impact on the patient response to treatment (i.e. SVRs in the model are not broken down by age or sex), but age and the proportion of men affect the all-cause mortality rates applied in the model, while patient weight has an impact on cost of treatment, as peginterferon alfa-2b and ribavirin dosage is weight related.

The health-state utilities have been derived from the UK Mild Hepatitis C Trial,[82] and a study of the cost-effectiveness of liver transplantation.[93] There is no systematic search for these values reported in the submission. The EQ-5D was completed by 130 patients within the Mild Hepatitis C Trial,[82] at 24 or 48 weeks post treatment or control. A linked observational study used cases recruited to the costing study in order to estimate the HRQoL for patients with moderate disease, compensated cirrhosis or decompensated cirrhosis. HRQoL for liver transplant patients and post-liver transplant health states was taken from a cost-effectiveness study of liver transplantation. This latter study also utilised the EQ-5D to estimate HRQoL in liver transplant patients; however, its applicability may be limited, as the included patients did not have HCV.

The model applies a disutility of 0.13 (owing to treatment-related adverse effects) to the utility score for treatment-eligible health states for the year in which patients undergo treatment. In their example, moderate HCV was assigned a baseline utility of 0.66, and this was reduced to 0.53 during treatment. This was based on the overall mean difference in EQ-5D utility score for treated and control patients at 12 or 24 weeks following randomisation in the UK Mild Hepatitis C Trial.[82] The disutility associated with treatment was adjusted for duration of treatment, so that a lower utility decrement would apply for patients (who fail to demonstrate an EVR) stopping treatment at 12 weeks.

The costs applied in the submission were made up of two components. Treatment-related costs (which consist of drug acquisition costs and monitoring of patients on treatment) were estimated

separately from health-state costs. Health-state costs include resource use associated with the management of progressive liver disease.

Drug usage for peginterferon alfa-2b was based on a dosage of 1.5 µg per kg per week and was assumed to be supplied in prefilled pens. As dosage of both peginterferon alfa-2b and ribavirin is weight based (*Table 24*) the MS needed to assume an average weight for each of the modelled patient populations. A mean weight of 80 kg was applied in the base-case analysis for the re-treated group, and of 63 kg in the HCV/HIV co-infected group. The values for the weight of the HCV/HIV co-infected group were taken from the Laguno study;[94] however, the default value in the MS is reported as 68.29 kg.

The drug acquisition costs for peginterferon alfa-2b and ribavirin adopted in the Schering-Plough submission[92] (taken from the *BNF*, No. 57, March 2009) are presented in *Tables 25* and *26* below. With an assumed body weight of 80 kg for re-treated patients, and assuming a preference for prefilled pens for peginterferon alfa-2b and tablets for ribavirin, the weekly treatment costs are £165.73 for peginterferon alfa-2b and £114.85 for ribavirin. The equivalent cost for the HCV/HIV co-infected patients is £118 for peginterferon alfa-2b and £91.88 for ribavirin.

TABLE 24 Peginterferon alfa-2b and ribavirin, weight-based dosage

	PEG α-2b		Ribavirin	
Body weight (kg)	Vial/pen strength (µg/ml)	Administer once weekly (ml)	Total daily dose (mg)	No. of capsules (200 mg)
< 40	50	0.5	800	4
40–50	80	0.5	800	4
51–64	80	0.5	800	4
65–75	100	0.5	1000	5
76–85	120	0.5	1000	5
86–105	150	0.5	1200	6
> 105	150	0.5	1400	7

PEG α, peginterferon alfa.

TABLE 25 Peginterferon alfa-2b acquisition cost

PEG α-2b (µg/bottle)	Pack costs (powder for reconstitution) (£)	Pack cost (prefilled pens) (£)
50	62.78	69.05
80	100.44	118.00
100	125.55	138.11
120	150.66	165.73
150	188.33	207.16

PEG α, peginterferon alfa.

TABLE 26 Ribavirin acquisition cost

Tablet size (mg)	Caps/pack	Pack cost (£)
200	84	275.65
200	140	459.42
200	168	551.30

The costs of initial investigations and monitoring included liver biopsy, an overnight stay in hospital for this procedure, and regular outpatient consultations and investigations. These costs were all taken from the Mild Hepatitis C Trial.[82] The initial investigations were calculated to cost £822.27 per patient assessed. As a result of interviews with clinicians, suggesting that between one and five patients would be assessed for each patient treated, this was then tripled to account for that (range 1–5). The monitoring costs of patients being treated was £489, which was inflated to £587.85 per patient treated (2007–8 values).

Costs for each disease state were again taken from the UK Mild Hepatitis C Trial,[82] or in the case of moderate and more severe disease from the observational costing study conducted within that trial.

The baseline population differs between the two patient groups modelled, and, for the majority of these characteristics, is based on the baseline population of the relevant clinical trials. The simulated cohort of re-treated patients has a mean age of 49 years, with 71% being male. Patient weight is assumed to be greater than 81 kg and it is assumed that 85% of re-treated patients have genotype 1 or 4 (the remainder with viral genotypes 2 and 3). This last assumption has an impact on outcome for the overall cohort of patients, as patients with viral genotypes 1 and 4 have a lower probability of SVR than those with viral genotype 2 or 3. For patients with HCV/HIV co-infection, the base-case characteristics are based on the RCT by Laguno and colleagues,[95] with a mean age of 40 years, and 68% being male. Patient weight is substantially lower at 63 kg, although as mentioned above this only affects the drug costs. While these characteristics have been drawn from clinical trials conducted in relevant subgroups, the MS does not discuss how relevant these characteristics may be to the population of UK patients with chronic HCV, in general, or how relevant they may be to the UK population of patients to be re-treated following non-response to, or relapse following, prior peginterferon treatment or those with HCV/HIV co-infection.

In both analyses, patients enter the model in one of three states – with mild HCV (33%), moderate HCV (33%) or compensated cirrhosis (34%). Each of these is a treatment-eligible health state and the probability of EVR or SVR is assumed to be equal for each possible starting state.

Model/cost-effectiveness results

The MS reports total costs and QALYs for a cohort of 100 re-treated patients and 100 HCV/HIV co-infected patients. Both cohorts include genotype 1, 2, 3 and 4 patients. To estimate costs and outcomes for these cohorts of mixed genotypes, treatment efficacy estimates (SVR and, where relevant, EVR) for genotype subgroups were used to estimate response for each subgroup. The overall results for the cohort were then calculated as weighted totals (based on the proportion of the total cohort in each subgroup). The model results are also presented as an average cost and average QALYs per patient for the cohort including all genotypes and for subgroups of genotypes 1 and 4 and of genotypes 2 and 3. The distribution of patients across viral genotypes is based on the populations recruited to the clinical trials used to derive the efficacy data for the model. The MS does not discuss how generalisable these proportions may be to UK populations of UK patients with chronic HCV infection.

Table 27 reports the base-case results, including the ICER, from the Schering-Plough model[92] for re-treatment of patients who did not respond or relapsed following previous interferon therapy and for HCV/HIV co-infected patients. Scatter plots showing the cost-effectiveness plane (incremental cost and incremental QALYs for peginterferon alfa-2b combination therapy) and CEACs are presented in a separate section of the MS reporting the results of the PSA.

The MS presents a further analysis for the cohort of re-treated patients, reporting separate analyses for previous relapsers, previous non-responders and previous treatment failures (although the definition of previous treatment failure is not very clear, and is described in the MS as referring to 'patients who could not be classified as relapsers or non-responders due to missing data or other reasons'). The results for these subgroups are presented in *Table 28* and show that previous non-responders have a lower QALY gain (and higher incremental cost) than previous treatment failures and relapsing patients.

The MS states that peginterferon alfa-2b in combination with ribavirin is cost-effective for adults with HCV/HIV co-infection and for patients whose previous treatment was unsuccessful. These conclusions draw on evidence from the base-case analyses presented above, from DSAs (where ICERs remained below £20,000 per QALY gained in the scenarios tested) and from PSAs where the probability for peginterferon alfa-2b being cost-effective, compared with no active treatment, for re-treating patients who did not respond or relapsed following previous interferon therapy was estimated at 95% at a willingness-to-pay threshold of £20,000 per QALY and the probability for peginterferon alfa-2b being cost-effective, compared with no active treatment, for HCV/HIV co-infected patients, was estimated at 98% at a willingness-to-pay threshold of £20,000 per QALY.

Outline appraisal of the cost-effectiveness analysis undertaken

The NICE reference case requirements (Schering-Plough) are shown in *Table 29*.

TABLE 27 Base-case results from thte Schering-Plough economic evaluation

Patient group	Genotypes	Treatment	Cost (£)	QALYs	ICER (£ per QALY gained)
Non-responders/ relapsers	1 + 4	No treatment	22,130	9.97	7177
		PEG α-2b + RBV	27,125	10.67	
	2 + 3	No treatment	22,130	9.97	783
		PEG α-2b + RBV	24,301	12.75	
	All	No treatment	22,130	9.97	4387
		PEG α-2b + RBV	26,666	11.01	
HCV/HIV co-infection	1 + 4	No treatment	24,494	10.90	1637
		PEG α-2b + RBV	27,790	12.91	
	2 + 3	No treatment	24,494	10.90	403
		PEG α-2b + RBV	25,645	13.75	
	All	No treatment	24,494	10.90	1077
		PEG α-2b + RBV	26,997	13.22	

PEG α, peginterferon alfa; RBV, ribavirin.

TABLE 28 Schering-Plough subgroup analysis for re-treatment of relapsed and non-responding patients

Patient group		Cost (£)	QALYs	ICER (£ per QALY gained)
Previous relapsers	No treatment	22,130	9.97	2048
	PEG α-2b + RBV	25,996	11.86	
Previous non-responders	No treatment	22,130	9.97	7581
	PEG α-2b + RBV	27,009	10.62	
Prior treatment failures	No treatment	22,130	9.97	3013
	PEG α-2b + RBV	26,157	11.31	

PEG α, peginterferon alfa; RBV, ribavirin.

TABLE 29 National Institute for Health and Clinical Excellence reference case requirements (Schering-Plough)

NICE reference case requirements[68]	Included in submission
Decision problem: as per the scope developed by NICE	✓
Comparator: alternative therapies routinely used in the UK NHS	✓
Perspective on costs: NHS and PSS	✓
Perspective on outcomes: all health effects on individuals	✓
Type of economic evaluation: cost-effectiveness analysis	✓
Synthesis of evidence on outcomes: based on a systematic review	?[a]
Measure of health benefits: QALYs	✓
Description of health states for QALY calculations: use of a standardised and validated generic instrument	✓
Method of preference elicitation for health-state values: choice-based method (e.g. TTO, SG, not rating scale)	✓
Source of preference data: representative sample of the public	✓
Discount rate: 3.5% pa for costs and health effects	✓

pa, per annum; SG, standard gamble; TTO, time trade-off.
a The Schering-Plough submission describes having performed a systematic review, but it is not clear whether all of the processes definitive of a systematic review have been conducted.

Outline review of modelling approach

Model structure/structural assumptions

No review of previous models has been reported, although the authors state that their model has adopted a similar structure to those used in previous assessment reports for NICE and for the economic evaluation alongside the Mild Hepatitis C trial.[82] The states representing more advanced liver disease in the model (compensated cirrhosis, decompensated cirrhosis, HCC and liver transplantation) are commonly accepted as distinct stages of progressive liver disease. These can be distinguished by their impact on QoL, resource use or excess mortality risk.

The effect of treatment is to induce an SVR in a proportion of patients, which is assumed to be a permanent cure. This agrees with previously published models in this patient population and is supported by long-term follow-up studies of patients achieving SVR on treatment. However, recent publications have highlighted a risk of liver cancer in patients in patients who have undergone SVR – particularly in patients with compensated cirrhosis at baseline, which, although lower than for non-responding patients, is not completely eradicated. As patients can enter the model in the compensated cirrhosis state (and receive treatment), excluding a transition from the SVR state (for patients who had developed cirrhosis at baseline) may overestimate the benefits from an SVR.

The model does not differentiate the SVR state according to patients' stage of disease prior to SVR. However, QoL data reported by the UK Mild Hepatitis C Trial[82] would suggest that there are differences in health-state utility for patients who enter the SVR state from mild and from moderate chronic HCV, and it may be more appropriate to structure the model to identify prior stage of disease (given that patients with compensated cirrhosis are eligible to receive treatment, as well as those with mild or moderate chronic HCV). Whether including only one SVR state is likely to over- or underestimate QoL or health-state utility will depend on the value assigned to the state.

Treatment-related adverse events are not included in the model, other than through the use of a decrement to utility while patients are on treatment. The exclusion of the costs of managing adverse events in the model is not discussed in the MS. However, the exclusion of treatment

costs for adverse events is in line with the approach adopted in previously published economic evaluations of antiviral treatment for chronic HCV.

The MS does not report any evidence of approaches to establish the internal consistency of the model or any evidence of external validation (by expert clinical opinion or by comparison with other published economic evaluations).

Data inputs

The main treatment effect applied in the model is the SVR for treated patients. For patients who failed to respond to or relapsed following previous interferon therapy the SVRs were taken from the EPIC3 study,[96] which is an open-label, single-arm study. The SVR for BSC was assumed to be zero for patients with moderate chronic HCV or compensated cirrhosis, but a low spontaneous SVR probability was applied for patients with mild chronic HCV. The spontaneous SVR probability is applied to both the treatment and the BSC cohorts. The spontaneous clearance of HCV is not discussed in the MS and the value (and derivation) of the transition probability is not included in table 35 of the MS, which lists the transition probabilities in the model. The MS does not discuss the relevance of data from the EPIC3 study,[96] with inclusion criteria that patients had prior failure (either non-response or relapse) on previous combination therapy with ribavirin and (non-pegylated or pegylated) interferon. The study does not appear strictly to meet the scope for the appraisal, which identifies the population considered for retreatment to be those previously treated with peginterferon alfa and ribavirin.

For patients with HCV/HIV co-infection, data on response to treatment were taken from an RCT reported by Laguno and colleagues,[95] which recruited treatment-naive (naive to combination therapy) patients with histologically verified liver disease who were HIV positive with controlled disease. In the trial, patients were randomised either to non-peginterferon combination therapy or peginterferon combination therapy. In the absence of a placebo or no active treatment control, the SVR for BSC was assumed to be zero for moderate chronic HCV, but with a low spontaneous SVR probability for patients with mild chronic HCV, as discussed earlier.

The EVR applied for re-treated patients was also derived from the EPIC3 study.[96]

The MS does not report any systematic or targeted searches to identify new data or to update parameter inputs derived from the model developed for our previous assessment[17] or that developed for the UK Mild Hepatitis C Trial,[82] nor does it report undertaking targeted searches for parameter inputs specific to the patient groups within the scope of this assessment.

The utility scores used for each disease state in the model were based on the values reported in the Mild Hepatitis C Trial,[82] which evaluated non-peginterferon alfa and ribavirin. These were generated in this trial using the standard EQ-5D time trade-off (TTO) tariff. The mean values are higher than those that have been used in the base-case analysis. All patients were assumed to experience a 0.13 reduction in utility due to treatment adverse effects. The disutility was applied to all patients receiving all treatment strategies, as there are no published data for patients' QoL while receiving peginterferon alfa. The drug costs were taken from the SPC. The Mild Hepatitis C Trial[82] was used to inform further costs: those taken into account included liver biopsy to assess eligibility for treatment and regular outpatient appointments and investigations for those who would not be eligible for further treatment. These costs were inflated to 2007–8 values. The discontinuation rates due to adverse events were taken from EPIC3[96] and Laguno and colleagues.[95] The transitions between health states came again from the Mild Hepatitis C Trial,[82] from the UK study of patients undergoing transplantation, and on a range of additional studies, referenced within the submission. It is unclear how these have been derived, and from which studies.

In this submission patients are distributed across the treatment-eligible states, but SVR/EVR are not adjusted according to the stage of disease in the base case or sensitivity analysis. This is despite evidence that SVR/EVR do vary according to disease severity, which is alluded to in the manufacturers' own submission. For example, on p. 16 the authors stated that key predictors of SVR included fibrosis level, and on p. 17 they stated that two significant predictors of SVR were identified, namely genotype and fibrosis score.

Assessment of uncertainty

Schering-Plough have tested response to therapy (where the EVR and SVR are varied) and drug dosing requirements (varying patient weight and drug administration method) in their DSA. In addition, the disutility and distribution of disease severity and distribution of genotype at baseline were varied. Two scenario analyses have also been reported: one in which the re-treatment group is presented as non-responders and relapsed patients and a further scenario in which discounting is removed.

The ICERs for both the re-treated group and the HCV/HIV co-infection group were both sensitive to variation in the EVR and SVR, and to changes in patient weight. The proportion of patients achieving EVR and SVR in the re-treatment group were varied between the upper and lower CIs from the included studies. The ICER in this group then changed from £4387 in the base-case analysis to £4842, where EVR proportion was 'low', and to £4003, where this was 'high'. The SVR was similarly varied, and the ICER changed to £5227 in the 'low-value' group and to £3615' in the 'high-value' group.

The peginterferon alfa-2b arm of the Scotto and colleagues[97] study was also used to calculate ICERs for re-treated patients. This resulted in a greatly increased ICER of £19,004 per QALY in the genotype 1 and 4 group, a decreased ICER of £2520 in the genotype 2 + 3 group, and £10,742 for all patients. The manufacturers state that this is owing to the re-treated patients in this study being previous non-responders.

Incremental cost-effectiveness ratios in the HCV/HIV co-infection group were sensitive to the SVR rate (the authors state that the EVR rate was unavailable in this group). Again, values for the sensitivity analysis were taken from the upper and lower CIs reported in the included study. The base-case ICER was £1077. In the 'low-value' group this increased to £4065 per QALY, and in the 'high-value' group, peginterferon alfa-2b was dominant. When the EVR and SVR values from the more recent Laguno and colleagues' RCT[94] were applied, the manufacturers report ICERs of £6140 per QALY in genotypes 1 and 4, £422 per QALY for genotypes 2 and 3, and £2311 for all genotypes. It is not clear if both EVR and SVR have been adjusted here.

Changes in the distribution of patients with different liver disease severity produced smaller variation in the ICERs in the re-treatment group. In the case of mild disease the percentage of patients decreases from 33% to 27%, for moderate disease this proportion decreased from 33% to 31%, and for compensated cirrhosis this proportion increased from 33% to 42%. This variation is quite small, and had the effect of decreasing the ICER to £3596 per QALY from £4387 per QALY.

A sensitivity analysis was performed on distribution of genotype at baseline. The treatment response of genotypes 1 and 4, and then 2 and 3, are applied to all patients. The treatment response of genotypes 1 and 4 applied to the entire cohort resulted in an ICER of £7176 per QALY, and that of genotypes 2 and 3 resulted in an ICER of £782, in the re-treatment group. In the HCV/HIV co-infected group, the ICERs became £1637 and £403. The ICERs are the same as those presented in the base-case analysis, and it is unclear what has been added to this analysis by the reporting of this scenario.

The first scenario analysis presented ICERs for the re-treatment 'subgroups': previous relapsers and non-responders to treatment. The base-case ICER for this group was £4387. For the 'previous relapser' group alone it was £2048 and for 'previous non-responders' alone in this scenario it was £7581, with the higher ICER thought by the authors to reflect the lower expected level of success in this group.

The second scenario analysis examined the effects of not discounting costs and outcomes. Where discounting is removed, the ICER is reduced to £1265 per QALY in the re-treatment group, and the intervention becomes dominant (more effective and less costly) in the HCV/HIV co-infection group.

Parameter uncertainty is also addressed in a PSA. The majority of parameters in the model are included in the PSA, including transition probabilities in the natural history model, health-state utilities, health-state costs, probability of discontinuing treatment as well as SVR and (where relevant) EVR. The choice of distribution applied to the parameters appears appropriate, using beta distributions for probabilities and utilities, and gamma distributions for costs. The electronic model appears to use an implementation of the Dirichlet distribution for sampling transition probabilities in the model that are competing risks (e.g. patients with compensated cirrhosis may remain in that state, may progress or may develop HCC), although this is not discussed in the submission. The written submission contains an appendix that lists the parameters included in the PSA, their mean value, SE and the choice of distribution, but not the parameterisation of the distribution.

The MS reports three PSAs for each patient group (re-treated and HCV/HIV co-infected patients), each based on 10,000 simulations. The first analysis applies to the overall cohort, followed by separate analysis for genotype subgroups (genotypes 1 and 4 and genotypes 2 and 3). Cost-effectiveness scatter plots are presented along with CEACs for each of these analyses. The MS also reports the probability of the intervention of interest being cost-effective at willingness-to-pay thresholds of £20,000 per QALY gained and at £30,000 per QALY gained. The presentation of the PSA appears generally to be in accordance with NICE methodological guidance[68] but does not report mean costs and outcome for the PSAs.

The key source of heterogeneity in the modelled populations, in terms of response to treatment, has been taken into account through the presentation of separate analyses for viral genotype. The MS has not considered another important source of heterogeneity, in terms of response to treatment, which is the stage of disease at treatment. Where trials have analysed SVR by stage of disease they tend to indicate that response is lower in patients with cirrhosis.

Summary of general concerns

- The Schering-Plough model appears to underestimate the SVR in each analysis, as a result of applying an unnecessary adjustment for treatment discontinuation, but appears to overestimate the utility gain through treatment by not applying an adjustment for treatment discontinuation:
  - The observed SVR for a given patient population (e.g. 38% for HCV/HIV co-infected patients with genotype 1 or 4) is applied to the proportion of patients expected to be in that population (63% of HCV/HIV co-infected patients are assumed to be genotype 1 or 4 in a cohort of 100 patients, i.e. 63 people) – therefore the expected number of SVRs is 24. This value is then multiplied by the probability of *not discontinuing* treatment (probability of discontinuing is 0.1731, therefore probability of not discontinuing = 1 – 0.1731), which gives a value of 20 (the number of SVRs adjusted for discontinuation), resulting in an SVR rate of 31.42% (20/63). As the original SVR rate of

38% was based on the observed data reported in the RCT by Laguno and colleagues,[95] adjusting by the discontinuation probability seems unnecessary.

- There is an implicit assumption that patients achieve an SVR immediately after treatment is initiated and therefore accrue health benefits on entering the model. It might be more reasonable to assume that transitions occur mid-cycle (essentially applying half-cycle adjustment). This would mean adjusting cycle lengths (currently annual) to cope with treatments that are significantly less than 52 weeks, or calculating a weighted combination of the utility for the initial state and the utility for the appropriate SVR state (weighted according to what proportion of the cycle is spent in the initial health state and what proportion in the SVR state).
- The model collapses the SVR state into one and therefore does not track whether patients have achieved SVR from mild HCV, moderate HCV or compensated cirrhosis. It applies the same health-state utility to patients achieving an SVR, irrespective of their stage of liver disease when treatment was initiated. This does not accord with utility data from the UK Mild Hepatitis C trial, which reported a lower mean utility for patients achieving SVR from moderate liver disease than those achieving SVR from mild liver disease.
- The model assumes that the SVR health-state cost is applied for all cycles the patient remains in the SVR state. This differs from the assumption applied in our previous assessment report,[17] where it was assumed that the SVR cost applied only for the year following treatment response.
- The model appears to have underestimated the cost of ribavirin (tables 31 and 32 of the MS report weekly cost of ribavirin as £16.41 for re-treated patients and £13.13 for HCV/HIV co-infected patients). These are derived using an estimated average cost per 200-mg tablet of ribavirin of approximately £3.28. However, the figures used in the MS are the daily, not weekly, costs.

Additional analyses undertaken by SHTAC

The assessment group undertook additional analyses using the manufacturer's model to address some of the concerns raised in the previous section. *Table 30* reports the results of the additional analyses undertaken for HCV/HIV co-infected patients. Removing treatment discontinuation from the calculation of the SVR probability and applying only the SVR health-state cost in year after SVR occurs reduces the ICER – making treatment for genotype 2 + 3 patients dominant. In contrast, correcting the calculation of ribavirin costs and splitting the SVR state to apply utility values that take account of disease stage prior to SVR increase the ICER.

The same SVR was applied to all treated patients in the manufacturer's model, regardless of stage of fibrosis. However, analyses of response to treatment, by stage of disease, typically suggest that treatment response is lower in patients with fibrosis. Ratios of the relative effectiveness of treatment for patients with fibrosis stages F2, F3 and F4 (derived using data reported in the MS for the EPIC3 study[95]) were used to examine the effect, on the cost-effectiveness results, of reducing the SVR for cirrhotic patients. This is labelled in *Table 30* as 'Adjust SVR for disease stage'.

Table 31 reports the results of the additional analyses undertaken for re-treated patients. Removing treatment discontinuation from the calculation of the SVR probability is less influential than in the analysis for HCV/HIV co-infected patients. Applying the SVR health-state cost in the year after SVR occurs reduces the ICER, while correcting the calculation of ribavirin costs and splitting the SVR state to apply utility values that take account of disease stage prior to SVR increase the ICER. Adjusting the SVR for disease stage has relatively little impact on the cost-effectiveness results. Overall, while these analyses suggest that the ICER for treating HCV/HIV co-infected patients with peginterferon alfa-2b combination therapy may be higher than in the manufacturer's base case, they do not substantially alter the conclusions from the analysis.

TABLE 30 Additional analysis for HCV/HIV co-infected patients

		Genotypes 1 + 4		Genotypes 2 + 3		All genotypes	
		Cost	Outcome	Cost	Outcome	Cost	Outcome
Original	BSC	24,494	10.90	24,494	10.90	24,494	10.90
	PEG	27,790	12.91	25,645	13.75	26,997	13.22
	ICER	*1637*		*403*		*1077*	
Use observed SVR (remove discontinuation)	BSC	24,494	10.90	24,494	10.90	24,494	10.90
	PEG	26,653	13.36	24,058	14.37	25,693	13.73
	ICER	*878*		*–126*		*423*	
Allow for different utility for SVR states	BSC	24,494	10.90	24,494	10.90	24,494	10.90
	PEG	27,790	12.21	25,645	12.77	26,997	12.42
	ICER	*2511*		*613*		*1645*	
Correct RBV cost	BSC	24,494	10.90	24,494	10.90	24,494	10.90
	PEG	31,407	12.91	29,262	13.75	30,613	13.22
	ICER	*3434*		*1671*		*2633*	
Only apply SVR cost for year following SVR	BSC	24,446	10.90	24,446	10.90	24,446	10.90
	PEG	25,747	12.91	22,814	13.75	24,661	13.22
	ICER	*646*		*–572*		*93*	
Adjust SVR for disease stage	BSC	24,494	10.90	24,494	10.90	24,494	10.90
	PEG	28,192	12.75	26,205	13.53	27,457	13.04
	ICER	*1992*		*649*		*1382*	
All together[a]	BSC	24,446	10.90	24,446	10.90	24,446	10.90
	PEG	28,296	12.41	24,942	13.06	27,055	12.65
	ICER	*2541*		*230*		*1488*	

PEG, peginterferon.

a Remove adjustment to SVR for discontinuation, differentiate SVR according to patients' stage of disease at baseline, correct error in ribavirin cost, apply SVR cost for 1 year only, and adjust SVR for disease stage (poorer response for cirrhotic patients).

Summary of manufacturers' models, compared with SHTAC model from previous assessment report

Table 32 summarises the transition probabilities used in the manufacturers' models and in our previous assessment of peginterferon alfa combination treatment for chronic HCV infection.[17] It is clear from the table that identical values have been used for the majority of transition probabilities modelling the natural history of progressive liver disease. These are primarily drawn from studies reported by Sweeting and colleagues,[18] Wright and colleagues[82] and Fattovich and colleagues.[98] The principal differences between the three models are that:

- Patients enter the Roche model with moderate HCV, so that the transition probability from mild-to-moderate disease is not relevant.
- The Schering-Plough model includes a small risk for non-cirrhotic patients (with moderate disease) developing HCC, based on a previously published economic evaluation by Bennett and colleagues.[76]
- The Schering-Plough model uses a higher excess mortality risk for HCC than is applied in the other models, based on a previously published economic evaluation[99] and cancer mortality statistics.[100]
- The Schering-Plough model uses a slightly higher probability for developing HCC for patients with cirrhosis. The value in *Table 32* is used in the electronic model, while a lower value of 0.014 (identical to that used by Roche and in our previous assessment) is reported in

TABLE 31 Additional analysis for patients re-treated following non-response to, or relapse from, previous treatment

		Genotypes 1 + 4		Genotypes 2 + 3		All genotypes	
		Cost	Outcome	Cost	Outcome	Cost	Outcome
Original	BSC	22,130	9.97	22,130	9.97	22,130	9.97
	PEG	27,125	10.67	24,301	12.75	26,666	11.01
	ICER	*7177*		*783*		*4387*	
Use observed SVR (remove discontinuation)	BSC	22,130	9.97	22,130	9.97	22,130	9.97
	PEG	26,974	10.72	23,723	12.95	26,445	11.09
	ICER	*6463*		*535*		*3881*	
Allow for different utility for SVR states	BSC	22,130	9.97	22,130	9.97	22,130	9.97
	PEG	27,125	10.40	24,301	11.74	26,666	10.62
	ICER	*11,586*		*1232*		*7006*	
Correct Rebetol cost	BSC	22,130	9.97	22,130	9.97	22,130	9.97
	PEG	29,324	10.67	28,221	12.75	29,145	11.01
	ICER	*10,336*		*2195*		*6785*	
Only apply SVR cost for year following SVR	BSC	22,093	9.97	22,093	9.97	22,093	9.97
	PEG	26,337	10.67	21,396	12.75	25,534	11.01
	ICER	*6099*		*–251*		*3329*	
Adjust SVR for disease stage	BSC	22,130	9.97	22,130	9.97	22,130	9.97
	PEG	27,301	10.61	24,975	12.53	26,923	10.92
	ICER	*8102*		*1114*		*5047*	
All together	BSC	22,093	9.97	22,093	9.97	22,093	9.97
	PEG	28,521	10.41	25,258	11.75	27,991	10.63
	ICER	*14,773*		*1781*		*9027*	

PEG, peginterferon.

tables included in the main submission document. This discrepancy is not explained in the submission or the electronic model.

Sustained virological responses used in manufacturers' models are shown below in *Table 33*.

Tables 34 and *35* report the health-state utility values applied in the three models and the impact on utility applied while patients are on treatment. The impact of structural assumptions in the models (particularly the inclusion of a single SVR state, which does not distinguish the stage of disease prior to SVR) and the selection of utility values applied to the SVR state have been discussed in the previous sections, appraising each of the manufacturer's models separately. *Table 34* shows that, in all but one case, identical utility values have been applied to the health states relating to more advanced liver disease, while there is considerable difference in the utility values applied to patients achieving an SVR [and, to a lesser extent, the HCV health state(s)].

Table 35 indicates that, although there are sizable differences in the utility values applied to the HCV and SVR health states, there is more agreement on the on-treatment utility reduction associated with peginterferon alfa and ribavirin. All three models have based their valuations on data from the UK Mild Hepatitis C Trial,[82] which reported health-state valuations for treated and untreated patients by stage of disease (adopted by Roche and in our previous assessment) and an overall mean difference in EQ-5D utility score, for treated and control patients, at 12 weeks or 24 weeks following randomisation (adopted by Schering-Plough).

Table 36 summarises the health-state costs applied in the three models. The main differences between the three models relate to:

TABLE 32 Transition probabilities in manufacturers' models, compared with SHTAC 2007

Health state							
From	**To**		**Roche**	**Schering-Plough**		**SHTAC[17]**	
SVR	SVR		a	a		a	
	Mortality	Liver disease	0	0		0	
		All cause	Age-/sex-specific	Age-/sex-specific		Age-/sex-specific	
HCV	SVR		See *Table 33*	See *Table 33*			
	HCV		a	a	0	a	0
				0.025	a	0.025	a
	CC		0.037	0	0.037	0	0.037
	HCC		0	0	0.001	0	0
	Mortality	Liver disease	0	0		0	
		All cause	Age-/sex-specific	Age-/sex-specific		Age-/sex-specific	
CC	SVR		0	See *Table 33*			
	CC		a	a		a	
	DC		0.039	0.039		0.039	
	HCC		0.014	0.01441		0.014	
	Mortality	Liver disease	0	0.02		0	
		All cause	Age-/sex-specific	Age-/sex-specific		Age-/sex-specific	
DC	DC		a	a		0.039	
	HCC		0.014	0.01441		0.014	
	LT		0.02	0.022		0.02	
	Mortality	Liver disease	0.129	0.130		0.130	
		All cause	0	Age-/sex-specific		Age-/sex-specific	
HCC	HCC		a	a		a	
	LT		0	0.02		0	
	Mortality	Liver disease	0.427	0.560		0.43	
		All cause	0	Age-/sex-specific		Age-/sex-specific	
LT	LT		a	a		a	
	Mortality	Liver disease	0.210	0.150		0.150	
		All cause	0	Age-/sex-specific		Age-/sex-specific	
Post LT	Post LT		a	a		a	
	Mortality	Liver disease	0.057	0.057		0.057	
		All cause	0	Age-/sex-specific		Age-/sex-specific	

CC, compensated cirrhosis; DC, decompensated cirrhosis; LT, liver transplant; post LT, post liver transplant.
a A default transition and is calculated as the complement of the other transition probabilities for each health state.

- Structural assumptions in the models (patients enter the Roche model with moderate HCV, so cost of mild HCV is not relevant, while both manufacturers collapse the SVR state and do not track the stage of disease prior to SVR).
- Sources of costs that have been inflated to current prices. Health-state costs in all three models are based on those reported for the UK Mild Hepatitis C Trial.[82] Roche have inflated health-state costs reported in our previous assessment (which had been inflated from 2002–3

TABLE 33 Sustained virological responses used in manufacturers' models

	Roche		Schering-Plough	
Patient group	**Genotype 1**	**Genotype non-1**	**Genotypes 1 + 4**	**Genotypes 1 + 3**
Non-responders (%)	13	21	48.65	69.95
Relapsed (%)	55	55	48.65	69.95
Shortened duration (%)	91[a]	89[b]	NA	NA
HIV co-infected (%)	40	40	38	53

NA, not available.
a Versus 97% for 48 weeks.
b Versus 94% for 24 weeks; unless otherwise noted, SVR in comparator group assumed to be 0%.

TABLE 34 Health-state utility in manufacturers' models, compared with SHTAC 2007

Health state	Roche	Schering-Plough	SHTAC[17]
SVR	0.91 (<45)	0.82	0.82 (from mild)
	0.85 (45–54)		0.72 (from moderate)
	0.80 (55–64)		0.60 (from CC)
	0.78 (65–74)		
	0.73 (≥75)		
HCV	0.66	0.77 (mild)	0.77 (mild)
		0.66 (moderate)	0.66 (moderate)
CC	0.55	0.55	0.55
DC	0.45	0.45	0.45
HCC	0.45	0.45	0.45
LT	0.45	0.45	0.45
Post LT	0.45	0.67	0.67

CC, compensated cirrhosis; DC, decompensated cirrhosis; LT, liver transplant; post LT, post liver transplant.

TABLE 35 Health-state utility on treatment in manufacturers' models, compared with SHTAC 2007

Health state	Roche	[a]Schering-Plough	[b]SHTAC[17]
Treatment-year utility	0.55	0.64 (mild)	0.66 (mild)
		0.53 (moderate)	0.55 (moderate)
		0.42 (CC)	0.44 (CC)

CC, compensated cirrhosis.
a Schering-Plough applied a utility decrement of 0.13 (the overall mean difference in EQ-5D utility score, for treated and control patients, at 12 or 24 weeks following randomisation) to the state-specific utilities for mild or moderate HCV and compensated cirrhosis, reported in *Table 34*.
b SHTAC adopted the state-specific on-treatment utilities for mild and moderate HCV reported by the UK Mild Hepatitis C Trial.[82] The trial did not provide treatment to cirrhotic patients, hence did not report a utility decrement for cirrhotic patients undergoing treatment with non-peginterferon alfa and ribavirin. The value for cirrhotic patients was assumed based on a 0.11 reduction (the difference between on-treatment and non-treatment utility values for mild and moderate HCV) from the state-specific utility (0.55).

to 2003–4 prices), whereas Schering-Plough inflated the original health-state costs reported for the trial. The discrepancies between the two sets of costs arises from slight adjustments that have been made to the HCHS Pay and Prices Index[85] over time.

TABLE 36 Health-state costs in manufacturers' models, compared with SHTAC 2007

Health state	Roche (2007–8)	Schering-Plough (year not stated)[a]	SHTAC[17] (2003–4 prices)	SHTAC (2007–8 prices)[b]
SVR	0	311	267 (mild)[c]	311
			267 (moderate)	311
			585.50 (CC)	684
HCV	843.38	166 (mild)	142 (mild)	166
		862 (moderate)	738 (moderate)	862
CC	1338.21	1368	1171	1368
DC	10,725.12	10,965	9385	10,964
HCC	9557.18	9770	8363	9770
LT	43,262.74	44,953	37,857	44,225
Post LT	1628.48	1665	1425	1665

CC, compensated cirrhosis; DC, decompensated cirrhosis; LT, liver transplant; post LT, post liver transplant.
a Inflated using HCHS (value and source not stated) from 2002–3 costs reported for UK Mild Hepatitis C Trial.[82]
b Costs from the UK Mild Hepatitis C Trial[82] inflated to 2007–8 prices using HCHS Pay and Prices Index.[85]
c In the SHTAC model, SVR health-state costs are applied only in the year following treatment (majority of cost is blood tests, in particular PCR to confirm SVR). The SVR cost for patients with compensated cirrhosis is applied for five years (cost is half of CC health-state cost).

Methods for SHTAC independent economic analysis

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

We adapted our previously published economic model[17] to estimate the cost-effectiveness of peginterferon alfa-2a and peginterferon alfa-2b for the treatment of chronic HCV, compared with current practice, in subgroups of adults who:

- were eligible for a shortened duration of treatment with peginterferon alfa-2a
- had failed to show a SVR on previous treatment with peginterferon alfa-2a or peginterferon alfa-2b
- were co-infected with HCV/HIV.

The perspective of the cost-effectiveness analysis is that of the NHS and PSS.

Strategies/comparators

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

- combination therapy with peginterferon alfa and ribavirin
- peginterferon alfa monotherapy (for those who cannot tolerate ribavirin).

The comparators for these interventions are BSC (for people who have been previously treated with peginterferon alfa and ribavirin in combination, and for people with HCV/HIV co-infection), or standard duration courses of combination therapy (for people who meet the criteria for receiving shortened courses of combination therapy with peginterferon alfa and ribavirin).

Model type and rationale for the model structure

The principal outcome of interest in the clinical trials systematically 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 we required an appropriate model of the natural history of chronic HCV. We adapted our previously published model,[17] which was used in NICE TA106.[33]

The state-transition diagram describing the health states within the model and the allowable transitions between these states is shown *Figure 2*. The diagram shows seven non-absorbing health states. For clarity, mortality (the absorbing state) has not been included. In this diagram, ellipses indicate health states and arrows indicate allowable transitions between health states. The shaded ellipses indicate health states with excess mortality risks attributable to chronic liver disease.

The diagram indicates that, in the absence of successful treatment, patients with chronic HCV or compensated cirrhosis may remain in their current health state or progress to more severe stages of liver disease. In our model the health state labelled SVR is divided into three, to differentiate the stage of disease (mild chronic HCV, moderate chronic HCV or compensated cirrhosis) prior to successful treatment. This is to take account of differences in risk for patients entering the SVR state from different stages of chronic liver disease (patients who achieve an SVR from mild or moderate chronic HCV are assumed to have the same risk of developing HCC as the general population, whereas those who had progressed to cirrhosis are assumed to have an excess risk of HCC). The SVR state is assumed to be a permanent condition, with no spontaneous reactivation of HCV infection, although individuals are not immune from re-infection (note: our analysis does not consider the impact of onwards transmission of, or re-infection with, HCV). 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 with mild or moderate chronic HCV, as well as those with compensated cirrhosis, face the same mortality risk as the general population. However, patients with decompensated liver disease, HCC and those who undergo liver transplantation face higher mortality rates related to their stage of liver disease than the general population. A dotted line has been drawn between HCC and liver transplantation to indicate that this transition is often not included in treatment models used for economic evaluations in chronic HCV, and has been excluded from this analysis.

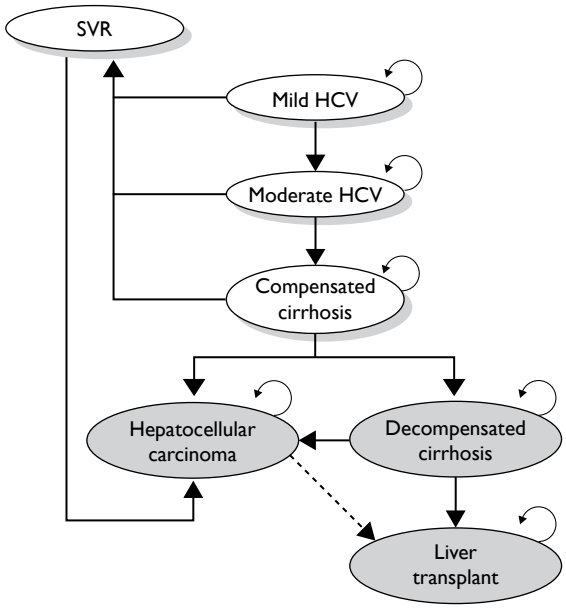

FIGURE 2 State-transition diagram for SHTAC economic model.

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.

Baseline cohort of adult chronic HCV patients

Baseline characteristics of the modelled populations were taken from a range of studies reporting relevant characteristics for UK populations of people with chronic HCV infection.[101,102] Patients eligible for shortened treatment durations and those with HCV/HIV co-infection have a mean age at entry to the model of 40 years, while re-treated patients have a mean age of 45 years. Seventy per cent of the cohort is male. The distribution of patients across stages of liver disease is taken from data reported from a clinical audit of patients attending for treatment at a liver unit at a London teaching hospital.[102] While this paper pre-dates current NICE guidance on the treatment of patients with chronic HCV infection, no other studies reporting the distribution of UK patients across stages of disease were identified in our searches. *Table 37* reports the distribution across disease stages for existing patients (taken to represent population of patients previously treated with peginterferon alfa and ribavirin) and new patients (taken to represent population of patients with HCV/HIV co-infection and those eligible to receive shortened courses of combination therapy).

TABLE 37 Distribution of patients across stages of disease

	Mild, % (*n*)	Moderate, % (*n*)	Cirrhosis, % (*n*)
Existing patients	33 (38)	35 (40)	32 (35)
New patients	46 (21)	44 (20)	10 (5)

Data sources

Effectiveness data

Table 38 reports the transition probabilities adopted in the natural history model for this economic evaluation. They represent the complete set of transition probabilities for the BSC comparator and are taken from our previous assessment report.[17]

The transition probabilities from mild-to-moderate disease, and from moderate disease to compensated cirrhosis, were derived for the economic evaluation undertaken alongside the UK Mild Hepatitis C Trial[82] and were based on a re-analysis of data from UK cross-sectional and longitudinal data sets. The remaining transition probabilities were taken from the literature on natural history and previous economic evaluations.[76,81,98,103] Targeted searches, undertaken as part of this assessment, did not identify new natural history evidence relating to progression or management of chronic HCV to update the model parameters.

Table 39 reports the treatment effects (proportion of patients achieving SVR) that have been applied, in the model, to estimate the effectiveness of peginterferon alfa and ribavirin combination therapy in the treatment strategies and patient subgroups being considered. The studies used to estimate the effectiveness of treatment have typically reported SVRs for all patients in the relevant subgroup and have not indicated the effect of stage of liver disease on response to treatment. For the base-case analyses we have assumed that the same SVR applies for patients with mild or moderate HCV, and for those patients with compensated cirrhosis. We examine the effect of cirrhosis, on reducing the response to treatment, in sensitivity analyses.

Sustained virological response estimates for patients receiving shortened courses of treatment are based on those used in our systematic review of clinical effectiveness (see *Chapter 4*, *Assessment of clinical effectiveness*). SVR estimates for patients co-infected with HCV/HIV were based on those reported from two recent systematic reviews of antiviral treatment in this patient group (further details can be found in *Appendix 9*). SVR estimates for patients re-treated following

TABLE 38 Transition probabilities for natural history model

Health state			
From	**To**	**Transition probability (SE)**	**Source**
Mild disease	Mild disease	[a]	
	Moderate disease	0.025 (0.004)	Wright and colleagues,[82] Grieve and colleagues[81]
Moderate disease	Moderate disease	[a]	
	CC	0.037 (0.007)	Wright and colleagues,[82] Grieve and colleagues[81]
CC	CC	[a]	
	DC	0.039 (0.010)	Fattovich and colleagues[98]
	HCC	0.014 (0.010)	Fattovich and colleagues[98]
DC	DC	[a]	
	HCC	0.014 (0.010)	Fattovich and colleagues[98]
	LT	0.020	Grieve and colleagues,[81] Siebert and colleagues[103]
	Death	0.130 (0.010)	Fattovich and colleagues[98]
HCC	HCC	[a]	
	Death	0.430 (0.030)	Fattovich and colleagues[98]
	LT	[a]	
LT	Death	Year 1 = 0.150, year 2 = 0.057	Grieve and colleagues,[81] Bennett and colleagues[76]

CC, compensated cirrhosis; DC, decompensated cirrhosis; LT, liver transplant.
a The default transition, calculated as the complement of the other transition probabilities for each health state.

TABLE 39 Effectiveness input parameters used in analysis

Patient group/ treatment strategy	Intervention	Genotype (s)	SVR		EVR	Withdrawal		Source
			Standard duration (*n*, %)	Shortened duration (*n*, %)		Standard duration (*n*, %)	Shortened duration (*n*, %)	
Shortened treatment duration	PEG α-2a + RBV	1	57/57 (100)	69/73 (94.5)	NA	14/154 (9.1)[a]	6/154 (3.1)[a]	Liu and colleagues[53]
			24/24 (100)	27/28 (96.4)		8/100 (8.0)[a]	3/100 (3.0)[a]	Yu and colleagues, 2007[54]
		2	85/87 (97.7)	43/43 (100)	NA	1/100 (1.0)[a]	0/50 (0.0)[a]	Yu and colleagues, 2008[55] von Wagner and colleagues[56]
		2/3	27/31 (87.1)	33/35 (94.3)		1/71 (1.4)[a]	0/71 (0.0)[a]	
	PEG α-2b + RBV	1	8/19, (42.1)	16/28, (57.1)	NA	7/255 (2.7)[a]	4/208 (1.9)[a]	Berg and colleagues[59]
			SVR (*n*, %)		EVR (*n*, %)	Withdrawal (*n*, %)		
Re-treated	PEG α-2a + RBV	1	18/142 (12.7)		21/142 (14.8)	20/316 (6.3)		Jensen and colleagues,[88] Roche[104]
		Non-1	6/29 (20.7)		10/29 (34.5)			
	PEG α-2b + RBV	1 + 4	162/1121 (14.5)		333/1121 (29.7)	89/1341 (6.6)		Schering-Plough[92]
		2 + 3	117/206 (56.8)		162/206 (78.6)			
HCV/HIV co-infected	PEG α-2a + RBV	1 + 4	64/245 (26.1)		NA	91/606 (15.0),[b] 99/606 (15.3)[c]		Kim and colleagues,[51] Zhao and colleagues[50]
		2 + 3	59/95 (62.1)					
	PEG α-2b + RBV	1 + 4	55/233 (23.6)					
		2 + 3	71/152 (46.7)					

NA, not available; PEG α, peginterferon alfa; RBV, ribavirin.

a Withdrawal data applies to all patients in trial arm – not the subgroup included in the analysis of efficacy. Data for the relevant subgroup not reported.

b Pooled data on patients discontinuing treatment owing to adverse effects from meta-analysis by Kim and colleagues.[51]

c Pooled data on patients discontinuing treatment owing to adverse effects and laboratory abnormalities from meta-analysis by Zhao and colleagues.[50]

non-response to, or relapse from, a previous course of peginterferon alfa-2a were taken from the trial by Jensen and colleagues,[88] supplemented with information from the Roche submission to NICE (see *Appendix 9*). SVRs for re-treatment with peginterferon alfa-2b were from the EPIC3 study,[96] as summarised in the Schering-Plough submission to NICE (see *Appendix 9*).

Health-state values/utilities

A systematic search of the literature (see *Appendix 2* for search strategy) and targeted searches did not find new utility data to update our model. In particular, the searches did not identify utility data that were specific to the patient populations within the scope of this assessment. As a result we have adopted the same utility values as for our previous assessment (*Table 40*).[17] These data are appropriate to the NICE reference case[68] for measuring and valuing health benefits, in that the QoL measurements were undertaken using the EQ-5D in patients with chronic HCV recruited to the UK Mild HCV Trial,[82] an observational study of patients with more severe liver disease conducted alongside the trial and a UK study of costs and outcomes following liver transplantation.[93] The QoL measurements were valued using a tariff derived in a general population.[84] While the use of these data has the advantage of consistency with those applied for the previous assessment,[17] they are not specific to the patient populations in the scope of this assessment. It may be argued that values derived from HCV mono-infected patients may overestimate the heath–state utility for HCV/HIV co-infected patients or that values from

TABLE 40 Health-state utilities

Health state	Utility
SVR (from mild disease)	0.82
SVR (from moderate disease)	0.72
Mild HCV	0.77
Treatment for mild HCV	0.66
Moderate HCV	0.66
Treatment for moderate HCV	0.55
Cirrhosis	0.55
DC	0.45
HCC	0.45
LT	0.45
Post LT	0.67

DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation; post LT, post liver transplantation.

treatment-naive patients (as in the UK Mild HCV Trial[82]) may not be representative of utilities for patients who have been previously treated.

Cost data

Intervention costs

Protocols describing the frequency and intensity of monitoring of patients being treated with peginterferon were developed for the previous assessment, based on clinical guidelines and discussion with hepatologists/specialist nurses at Southampton University Hospitals Trust, and are described in full in the previous assessment report.[17] Additional costs for patient management (including the initial evaluation of a new patient with chronic HCV, 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 costs have been uprated to 2007–8 values (from 2003–4 prices) using the HCHS Pay and Prices Index[85] and are reported in *Table 41*.

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. 58, September 2009.[47]

Drug costs for peginterferon alfa-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 £126.91. The total drug cost for a 24-week course of treatment for genotype 2/3 patients is £3046 for monotherapy, and for 48 weeks is £6092. Drug costs for ribavirin (Copegus) for dual therapy with peginterferon alfa-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. Patients co-infected with HCV and HIV also receive 800 mg of ribavirin per day, irrespective of genotype. A 168-tab packet of 200-mg tablets costs £444.43. This corresponds to a weekly cost of £111 for genotype 1 (based on an average body weight of 79 kg) and £74 for genotype 2/3. The total drug costs estimated for 24 weeks of dual therapy are £4824, and are £11,425 for 48 weeks of dual therapy (or £9647 for HCV/HIV co-infected patients having 48 weeks of dual therapy).

Drug costs for peginterferon alfa-2b (ViraferonPeg) were calculated for a patient weighing 79 kg (at a dosage of 1.5 µg/kg for dual therapy). Weekly costs were estimated as the unit cost for the appropriate dosage using a pre-filled pen (£162.60 for dual therapy). The total drug cost for a 24-week course of treatment is £3902 and for 48 weeks is £7805. Dosage of ribavirin (Rebetol), used in dual therapy with peginterferon alfa-2b, is also weight based (*Table 42*). Drug costs for ribavirin, in combination with peginterferon alfa-2b, were calculated for a dosage of 1000 mg per day, based on an average body weight of 79 kg. A 168-tab packet of 200-mg tablets costs £327.60, which corresponds to a weekly cost of £68. Combined with the costs estimated above this gives a total drug cost for combination therapy (peginterferon alfa-2b plus ribavirin) of £5540 for 24 weeks of treatment for genotype 2/3 patients, and £11,081 for 48 weeks of treatment for genotype 1 patients.

TABLE 41 On-treatment monitoring costs by duration of treatment

On-treatment monitoring (weeks)	Cost (£)
12	649
16	782
24	792
48	1051
72	1039

TABLE 42 Weight-based dosing of ribavirin in combination with peginterferon alfa-2b

Body weight (kg)	Total daily dose of Rebetol (mg)
< 65	800
65–85	1000
86–105	1200
> 105	1400

Health-state costs

Health-state costs for SVR, chronic HCV, compensated cirrhosis, decompensated cirrhosis and HCC have been taken from the observational study conducted during the UK Mild HCV Trial (*Table 43*).[82] Costs for liver transplantation and post liver transplantation were taken from a Department of Health-funded study of the costs of liver transplantation.[105] Costs for 2002–3 have been updated to 2007–8 costs using the HCHS Pay and Prices Index.[85]

TABLE 43 Health-state costs

Health state	Cost (£/year), 2007–8 prices
SVR	311
Mild chronic HCV	142
Moderate chronic HCV	862
CC	1368
DC	10,964
HCC	9770
LT	44,225
Post LT	1665

CC, compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation; post LT, post liver transplantation.

Discounting of future costs and benefits

A discount rate of 3.5% was applied to future costs and benefits, in line with current methodological guidance from NICE.[68] Discount rates of 0% (for both costs and benefits), 6% (for costs) and 1.5% (for benefits) were applied in the sensitivity analyses.

Presentation of results

We report findings on the cost-effectiveness of interventions based on analysis of a cohort of patients with age, sex and genotype characteristics as reported above (see *Baseline cohort of adult chronic HCV patients*). For HCV/HIV co-infected patients and re-treatment of patients who failed to respond to, or relapse from, prior peginterferon alfa therapy, the interventions assessed in this report are compared with BSC (i.e. without any form of interferon alfa therapy) as specified in the NICE scope. For patients who are eligible for shortened courses of peginterferon alfa, results are presented in comparison with the usual duration of treatment.

We report the results of these comparisons 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 PSA. Probability distributions are assigned to the point estimates used in the base-case analysis. The point estimates for state transitions and treatment effects are reported in *Tables 38* and *39*, for health-state utilities in *Table 40* and for health-state costs in *Table 43*. *Appendix 10* 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.

Results of SHTAC independent economic analysis

Shortened treatment duration

Peginterferon alfa-2a

Costs and outcomes modelled for patients who were eligible for shortened duration of treatment with peginterferon alfa-2a and ribavirin combination therapy are presented in *Table 44* for genotype 1 patients and in *Table 45* for patients with genotype 2 or 3. As it was not considered appropriate to conduct a meta-analysis of RCTs, we present separate results for each trial included in our systematic review of clinical effectiveness (with the exception of the RCT by Mangia and colleagues,[52] which used both peginterferon alfa-2a and alfa-2b within the same trial; as the two drugs are considered pharmacologically different, we present cost-effectiveness estimates for peginterferon alfa-2a based on RCTs of alfa-2a, and peginterferon alfa-2b based on RCTs of alfa-2b). The comparator in each of the analyses is the standard duration of peginterferon alfa-2a combination therapy (48 weeks for genotype 1 patients and 24 weeks for

TABLE 44 Base-case cost-effectiveness for shortened treatment duration using peginterferon alfa-2a and ribavirin combination therapy in genotype 1 patients

RCT	Treatment duration	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Liu and colleagues 2008[53]	Standard (48 weeks)	14,206	20.86	15.68	
	Shortened (24 weeks)	9399	20.76	15.54	
	Incremental	–4807	–0.11	–0.14	34,510
Yu and colleagues 2008[54]	Standard (48 weeks)	14,206	20.86	15.68	
	Shortened (24 weeks)	8994	20.80	15.60	
	Incremental	–5212	–0.07	–0.08	64,880

TABLE 45 Base-case cost-effectiveness for shortened treatment duration using peginterferon alfa-2a and ribavirin combination therapy in genotype 2 or 3 patients

RCT	Treatment duration	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Yu and colleagues 2007[55]	Standard (24 weeks)	7834	20.82	15.64	
	Shortened (16 weeks)	5728	20.86	15.72	
	Incremental	–2107	0.04	0.08	Shortened duration dominates
von Wagner and colleagues 2005[56]	Standard (24 weeks)	10,089	20.61	15.31	
	Shortened (16 weeks)	6943	20.75	15.54	
	Incremental	–3146	0.14	0.23	Shortened duration dominates

patients with genotype 2 or 3). The tables report total costs (antiviral treatment and supportive care), health outcomes (in terms of life-years and QALYs) and the incremental cost-per-QALY ratios. Costs and health outcomes are discounted at 3.5%.

In both of the included trials of shortened treatment duration for genotype 1 patients, standard 48-week treatment was associated with an SVR of 100%. However, this high SVR is only applicable to the subgroup of patients who had baseline LVL (< 800,000 IU/ml in the trial by Liu and colleagues[53] and < 400,000 IU/ml in the trial by Yu and colleagues, 2008[54] – the SPC for peginterferon alfa-2a[42] defines LVL as ≤ 800,000 IU/ml at baseline) and who also demonstrate an RVR. Shortened treatment duration was associated with a slight reduction in SVR (to 94% in the trial by Liu and colleagues[53] and 96% in the trial by Yu and colleagues[54]). Shorter duration of 24 weeks of treatment is associated with a reduction in total costs between £4800 and £5200. This is primarily due to the reduction in drug acquisition costs, although there is some additional reduction in cost of on-treatment monitoring. While the small reduction in SVR means that there are some additional costs associated with disease progression for the cohort of patients receiving shorter duration of treatment, these are not sufficient to offset the cost reduction associated with the shorter duration of treatment.

Given that the SVR is lower, and therefore there is a greater risk of progressive liver disease, there is a reduction in total QALYs between 0.08 and 0.14 (depending on trial) associated with shorter duration of treatment. This is not offset by the QoL impact of treatment-related adverse events estimated for the cohort of patients receiving shorter duration of treatment. As total costs and total QALYs are reduced in the cohort of patients receiving shorter duration of treatment, the ICER is positive but is located in the south-west (cost- and outcome-reducing) quadrant of the cost-effectiveness map rather than the more familiar north-east (cost-increasing and

outcome-gaining) quadrant. This has implications for the interpretation of the results from the base-case (deterministic) analysis and from the PSA, including the interpretation of the CEACs.

In both of the included trials for genotype 2 or 3 patients, shortened treatment duration was associated with a higher SVR than was the case for standard treatment. Shorter duration of treatment is associated with a reduction in total costs between £2100 and £3150. This is primarily due to the reduction in drug acquisition costs and a reduction in the cost of on-treatment monitoring. Given that the SVR is higher for the shorter duration of treatment, there are small reductions in total cost associated with a reduced risk of disease progression for the cohort of patients receiving shorter duration of treatment. The higher SVR for the shorter duration of treatment also results in improvements in modelled outcomes associated with shorter duration of treatment so that the strategy of shortened treatment duration for this group of patients dominates standard duration treatment.

Deterministic sensitivity analysis

Table 46 reports the results of a DSA for genotype 1 patients who were eligible for shortened treatment duration, and *Table 47* reports the results for genotype 2/3 patients. These are predominantly univariate sensitivity analyses – that is, varying one parameter at a time, from its base-case value, leaving all other variables unchanged. The table is divided to distinguish between analyses undertaken owing to structural uncertainties in the model, uncertainties over the composition of the baseline cohort and uncertainty over parameter values.

The DSA suggests that the results are robust to a change in structural assumptions (allowing spontaneous SVR from the mild chronic HCV state), the proportion of the baseline cohort that is male and the cost associated with the SVR health state. Reducing drug acquisition costs has the effect of reducing the cost-effectiveness of shortened treatment duration, as it reduces the cost saving between standard and shortened treatment duration while the outcome difference is unchanged.

The greatest variability in ICERs is associated with changes in two assumptions regarding baseline characteristics of the cohort of treatment-eligible patients. Increasing the mean age of patients at the start of the simulation up to 15 years leads to an approximate doubling of the ICER. This occurs because the QALY difference between the standard and shortened treatment duration reduces rapidly [from –0.14 at a starting age of 40 years to –0.08 at a starting age of 55 years (a reduction of 43%) using efficacy data from the RCT by Liu and colleagues[53]]. The difference in costs between standard and shortened treatment duration is less responsive to changes in starting age [from –£4807 at a starting age of 40 to –£5098 at a starting age of 55 (a reduction of 6%) using the same efficacy data]. Alternative assumptions regarding the stage of liver disease in patients starting treatment also has a large impact on the ICER, with shortened treatment duration being more cost-effective in patients with less severe disease than in those with cirrhosis. This arises because, all other things being equal, the higher the proportion of a cohort starting the simulation with cirrhosis, the greater the proportion that will progress to advanced liver disease. As a result, the penalty (in terms of a reduction in total QALYs) associated with a lower SVR for shortened treatment duration will be greater in cohorts that contain a higher proportion of patients with cirrhosis.

The pattern of results for genotype 2/3 patients, reported in *Table 47*, is similar to those for genotype 1 patients. The results are largely insensitive to changes in input parameters, other than baseline assumptions relating to age and stage of disease at start of treatment. Shortened treatment duration remains dominant in all the scenarios tested in *Table 47*, using efficacy data from either of the included trials.

TABLE 46 Deterministic sensitivity analysis for genotype 1 patients eligible for shortened treatment duration using peginterferon alfa-2a and ribavirin combination therapy

	Genotype 1					
	Liu and colleagues[53]			Yu and colleagues 2008[54]		
	Incremental cost (£)	Incremental QALY	ICER	Incremental cost (£)	Incremental QALY	ICER
Base case	–4807	–0.14	34,510	–5212	–0.08	64,880
Structural uncertainty						
Spontaneous SVR from mild (0.002)	–4851	–0.13	37,420	–5241	–0.07	70,779
Spontaneous SVR from mild (0.010)	–4831	–0.13	36,033	–5228	–0.08	67,953
Discount cost and outcome at 0%	–3605	–0.38	9543	–4429	–0.24	18,785
Discount cost at 6%, outcome at 1.5%	–5187	–0.24	21,447	–5460	–0.15	37,096
Baseline cohort characteristics						
Cohort 80% male	–4813	–0.14	34,917	–5216	–0.08	65,702
Cohort 40% male	–4788	–0.14	33,281	–5200	–0.08	62,412
Change average age of cohort at start of simulation (base case 40 years old)						
–10 years	–4674	–0.18	26,429	–5126	–0.10	48,901
+5 years	–4892	–0.12	41,051	–5268	–0.07	78,362
+10 years	–4989	–0.10	50,551	–5331	–0.05	98,940
+15 years	–5098	–0.08	65,021	–5402	–0.04	132,866
Change distribution of cohort across disease stages at start of simulation						
Cohort 100% mild chronic HCV	–5396	–0.09	57,661	–5597	–0.05	110,708
Cohort 100% moderate HCV	–4415	–0.17	26,641	–4957	–0.10	50,807
Cohort 100% CC	–3817	–0.23	16,371	–4567	–0.14	32,270
Parameter uncertainty						
Assume SVR is 25% lower in patients with CC	–4860	–0.13	36,627	–5247	–0.08	69,001
Assume SVR is 50% lower in patients with CC	–4914	–0.13	38,964	–5282	–0.07	73,614
Cohort 100% CC, assume SVR is 25% lower in patients with CC	–4356	–0.17	26,023	–4918	–0.10	49,855
Cohort 100% CC, assume SVR is 50% lower in patients with CC	–4894	–0.10	48,177	–5269	–0.06	94,485
Transition probability from mild-to-moderate disease = 0.04	–4733	–0.15	31,168	–5164	–0.09	58,333
Transition probability from moderate disease to CC = 0.073	–4650	–0.18	26,516	–5110	–0.10	49,205
Cost of SVR state = £0	–4790	–0.14	34,392	–5201	–0.08	64,747
Reduce cost of PEG α-2a by 20%	–4197	–0.14	30,136	–4603	–0.08	57,298
Reduce cost of PEG α-2a by 30%	–3893	–0.14	27,949	–4298	–0.08	53,506
Reduce cost of RBV by 20%	–4273	–0.14	30,681	–4679	–0.08	58,242
Reduce cost of RBV by 20%	–4007	–0.14	28,766	–4412	–0.08	54,922

PEG α, peginterferon alfa; RBV, ribavirin.

TABLE 47 Deterministic sensitivity analysis for genotype 2 or 3 patients eligible for shortened treatment duration using peginterferon alfa-2a and ribavirin combination therapy

	Genotype 2			Genotype 2/3		
	Yu and colleagues 2007[55]			von Wagner and colleagues 2005[56]		
	Incremental cost (£)	Incremental QALY	ICER	Incremental cost (£)	Incremental QALY	ICER
Base case	–2107	0.08	–26,000	–3146	0.23	–13,555
Structural uncertainty						
Spontaneous SVR from mild (0.002)	–2088	0.08	–27,124	–3088	0.22	–14,071
Spontaneous SVR from mild (0.010)	–2096	0.08	–26,595	–3115	0.23	–13,827
Discount cost and outcome at 0%	–2610	0.18	–14,416	–4722	0.55	–8664
Discount cost at 6%, outcome at 1.5%	–1947	0.12	–15,695	–2647	0.37	–7220
Baseline cohort characteristics						
Cohort 80% male	–2104	0.08	–26,165	–3138	0.23	–13,632
Cohort 40% male	–2115	0.08	–25,495	–3171	0.24	–13,319
Change average age of cohort at start of simulation (base case 40 years old)						
–10 years	–2162	0.10	–22,343	–3320	0.28	–11,801
+5 years	–2071	0.07	–28,532	–3034	0.21	–14,752
+10 years	–2030	0.06	–31,720	–2906	0.18	–16,250
+15 years	–1984	0.06	–35,763	–2763	0.15	–18,153
Change distribution of cohort across disease stages at start of simulation						
Cohort 100% mild chronic HCV	–1859	0.06	–30,058	–2372	0.17	–13,780
Cohort 100% moderate HCV	–2271	0.09	–24,655	–3660	0.27	–13,721
Cohort 100% CC	–2522	0.12	–20,940	–4444	0.36	–12,507
Parameter uncertainty						
Assume SVR is 25% lower in patients with CC	–2084	0.08	–26,629	–3075	0.22	–13,763
Assume SVR is 50% lower in patients with CC	–2061	0.08	–27,303	–3005	0.21	–13,987
Cohort 100% CC, assume SVR is 25% lower in patients with CC	–2296	0.09	–24,734	–3737	0.27	–13,895
Cohort 100% CC, assume SVR is 50% lower in patients with CC	–2070	0.07	–31,740	–3031	0.18	–16,594
Transition probability from mild-to-moderate disease = 0.04	–2137	0.09	–24,769	–3243	0.25	–13,045
Transition probability from moderate disease to CC = 0.073	–2172	0.10	–22,591	–3352	0.28	–11,994
Cost of SVR state = £0	–2113	0.08	–26,085	–3168	0.23	–13,648
Reduce cost of PEG α-2a by 20%	–1903	0.08	–23,494	–2943	0.23	–12,680
Reduce cost of PEG α-2a by 30%	–1802	0.08	–22,241	–2842	0.23	–12,243
Reduce cost of RBV by 20%	–1988	0.08	–24,537	–3028	0.23	–13,045
Reduce cost of RBV by 20%	–1929	0.08	–23,806	–2968	0.23	–12,789

CC, compensated cirrhosis; PEG α, peginterferon alfa; RBV, ribavirin.

As the included trials give contradictory results (with shortened duration less effective than standard duration for genotype 1 patients, but more effective for genotype 2/3 patients) and, in the case of genotype 2/3 patients, potentially counterintuitive results, we conducted an additional scenario analysis on the impact of the difference in SVR on the cost-effectiveness results, assuming that the SVR for shortened treatment duration is less than or equal to that for standard treatment duration (*Table 48*).

This suggests that shortened treatment duration may be a highly cost-effective option, where there is no difference (or a very small difference) in SVR between shortened and standard treatment duration, but as the SVR difference increases the cost reduction decreases and the QALY loss increases rapidly – particularly in the case of genotype 2/3 patients.

TABLE 48 Scenario analyses for difference in SVR for shortened treatment duration using peginterferon alfa-2a and ribavirin combination therapy, compared with standard treatment – impact on cost-effectiveness estimates

SVR difference (%)	Incremental cost (£)	Incremental QALY	ICER
Genotype 1			
0	–5971	0.03	–199,047
1	–5759	0.00[a]	6,442,219
3	–5334	–0.06	85,091
5	–4908	–0.12	39,435
Genotype 2/3			
0	–1618	0.01	–161,785
1	–1405	–0.02	67,257
3	–980	–0.08	11,854
5	–555	–0.14	3841

a The incremental QALY value of 0.00 appears in the table owing to rounding (to two decimal places). The value here is a very small negative number (–0.0009) hence the positive ICER.

Probabilistic sensitivity analysis

In a PSA, where the probabilities of achieving SVR, health-state costs, health-state utility values and transition probabilities for the natural history parameters were sampled probabilistically, shortened duration of treatment with peginterferon alfa-2a and ribavirin combination therapy was generally associated with reduced QALYs. For genotype 1 patients incremental QALYs associated with shortened duration of treatment were negative for the majority of simulations – 95% of simulations using efficacy data (proportion of patients with SVR) from Liu and colleagues,[53] and 99.5% of simulations using efficacy data from Yu and colleagues.[54] The opposite is true in the analysis of genotype 2 or 3 patients. Approximately 2% of simulations were associated with negative incremental QALYs, for genotype 2 patients, using efficacy data from Yu and colleagues,[55] whereas none of the simulations resulted in negative incremental QALYs using efficacy data from von Wagner and colleagues.[56] Incremental costs associated with shortened duration of treatment were negative in all simulations – ranging from –£2500 to –£6000 for genotype 1 patients and from –£550 to –£5200 for genotype 2/3 patients. *Table 49* reports summary information for the PSAs and *Figures 3–6* show the scatter plots for each analysis, including 95% confidence ellipses.

In this analysis, shortened duration of treatment using peginterferon alfa-2a and ribavirin combination therapy for genotype 1 patients had a probability of being cost-effective [compared with the standard duration (48 weeks) of treatment] of 83% at a willingness-to-pay threshold of £20,000 per QALY and 59% at a willingness-to-pay threshold of £30,000, using efficacy data from the trial reported by Liu and colleagues[53] (*Figure 7*). The equivalent values using efficacy data from the trial reported by Yu and colleagues 2008[54] are 100% at willingness-to-pay thresholds of £20,000 and £30,000 per QALY.

TABLE 49 Mean costs and outcomes (percentile-based 95% CIs) for shortened treatment duration using peginterferon alfa-2a and ribavirin combination therapy from PSA

RCT	Treatment duration	Lifetime costs (£)	QALYs
Genotype 1			
Liu and colleagues 2008[53]	Standard duration	14,566 (14,020 to 15,708)	15.60 (14.39 to 16.77)
	Shortened duration	9,815 (8546 to 12,040)	15.45 (14.32 to 16.56)
	Incremental	–4752 (–5582 to –3658)	–0.14 (–0.32 to –0.02)
Yu and colleagues 2008[54]	Standard duration	15,062 (14,067 to 17,639)	15.55 (14.38 to 16.71)
	Shortened duration	9701 (8309 to 12,538)	15.50 (14.36 to 16.66)
	Incremental	–5361 (–5810 to –4922)	–0.06 (–0.13 to 0.01)
Genotype 2			
Yu and colleagues 2007[55]	Standard duration	8056 (7360 to 9300)	15.61 (14.48 to 16.78)
	Shortened duration	6201 (5577 to 7659)	15.65 (14.49 to 16.84)
	Incremental	–1855 (–2019 to –1,576)	0.04 (0.00 to 0.07)
Genotypes 2 + 3			
von Wagner and colleagues 2005[56]	Standard duration	10,072 (8048 to 13,552)	15.33 (14.25 to 16.42)
	Shortened duration	6931 (5794 to 9160)	15.56 (14.41 to 16.66)
	Incremental	–3141 (–4287 to –2242)	0.23 (0.08 to 0.40)

For patients with genotypes 2 and 3, the probability of being cost-effective [compared with the standard duration (24 weeks) of treatment] was 100% at willingness-to-pay thresholds of £20,000 and £30,000 per QALY, using efficacy data from either the trial reported by Yu and colleagues, 2007[55] or the trial by von Wagner and colleagues[56] (*Figure 8*). This reflects the proportion of simulations located in the south-east quadrant of the cost-effectiveness map (where the intervention dominates the comparator) – see *Figures 5* and *6*.

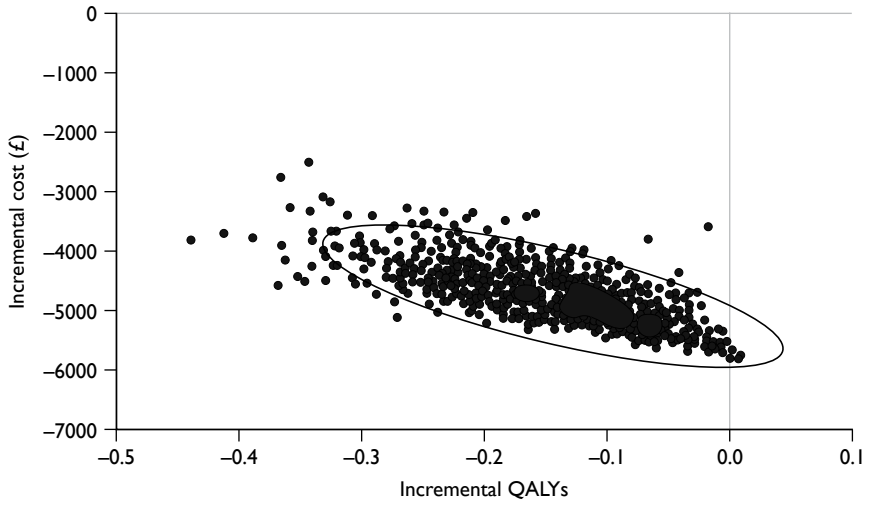

FIGURE 3 Cost-effectiveness plane for genotype 1 patients – incremental cost and incremental QALYs for shortened treatment duration using peginterferon alfa-2a and ribavirin combination therapy (24 vs 48 weeks of treatment) – efficacy from Liu and colleagues.[53]

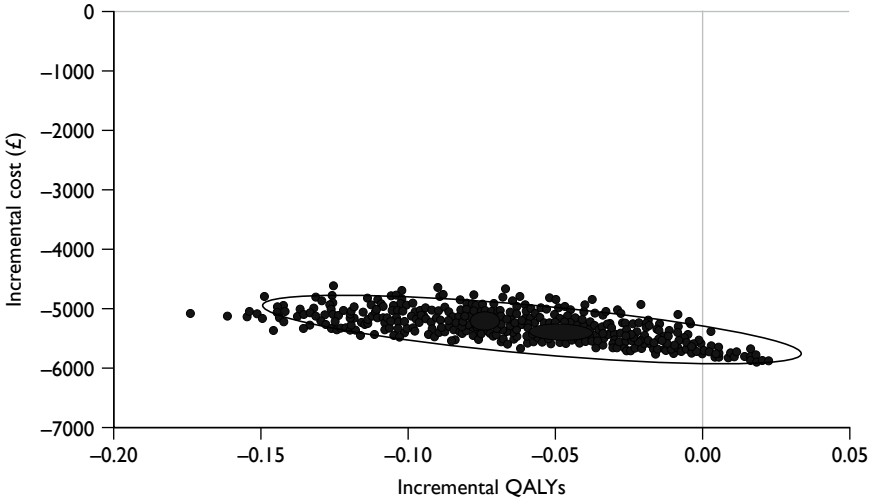

FIGURE 4 Cost-effectiveness plane for genotype 1 patients – incremental cost and incremental QALYs for shortened treatment duration using peginterferon alfa-2a and ribavirin combination therapy (24 vs 48 weeks of treatment) – efficacy from Yu and colleagues.[54]

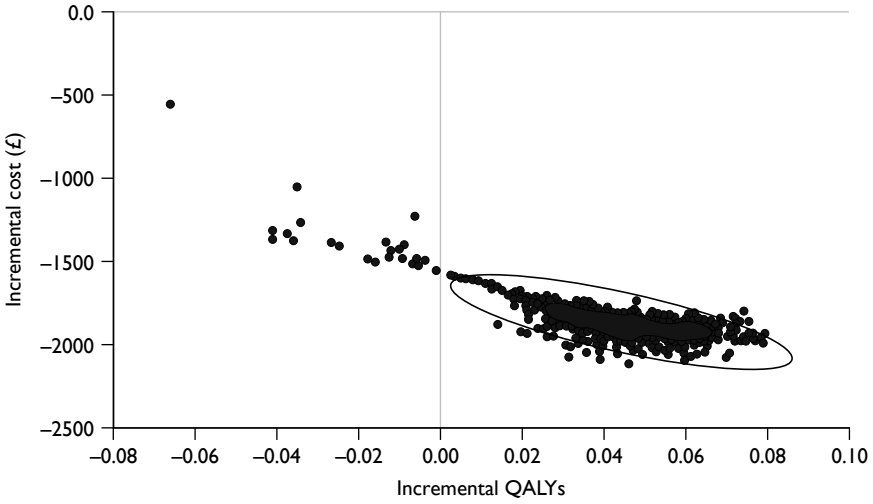

FIGURE 5 Cost-effectiveness plane for genotype 2 patients – incremental cost and incremental QALYs for shortened treatment duration using peginterferon alfa-2a and ribavirin combination therapy (16 vs 24 weeks of treatment) – efficacy from Yu and colleagues.[55]

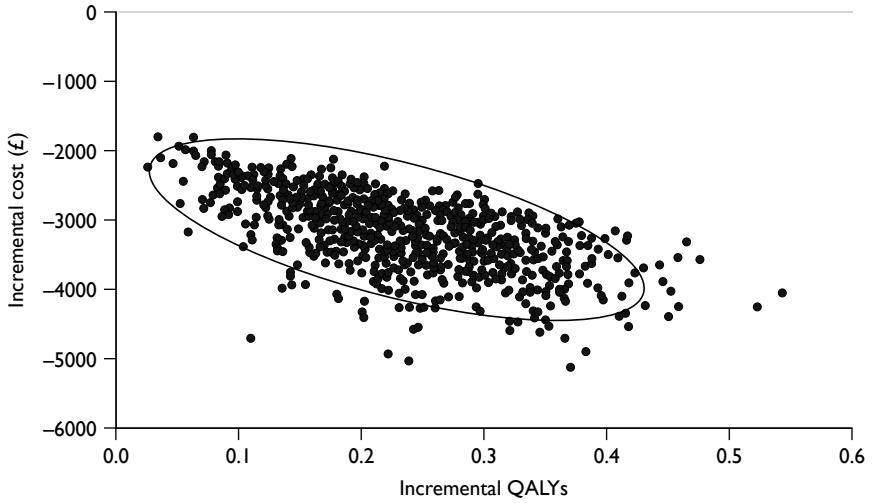

FIGURE 6 Cost-effectiveness plane for genotypes 2/3 patients – incremental cost and incremental QALYs for shortened treatment duration using peginterferon alfa-2a and ribavirin combination therapy (16 vs 24 weeks of treatment) – efficacy from von Wagner and colleagues.[56]

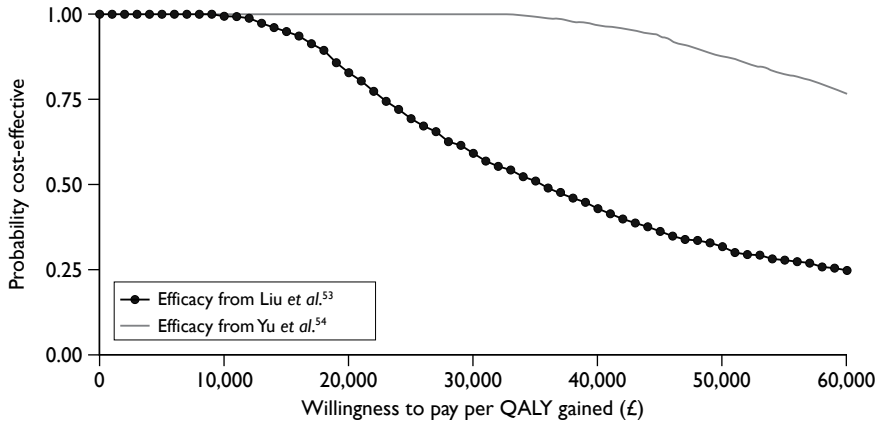

FIGURE 7 Cost-effectiveness acceptability curves for shortened treatment duration with peginterferon alfa-2a and ribavirin combination therapy (24 vs 48 weeks of treatment) for genotype 1 patients.

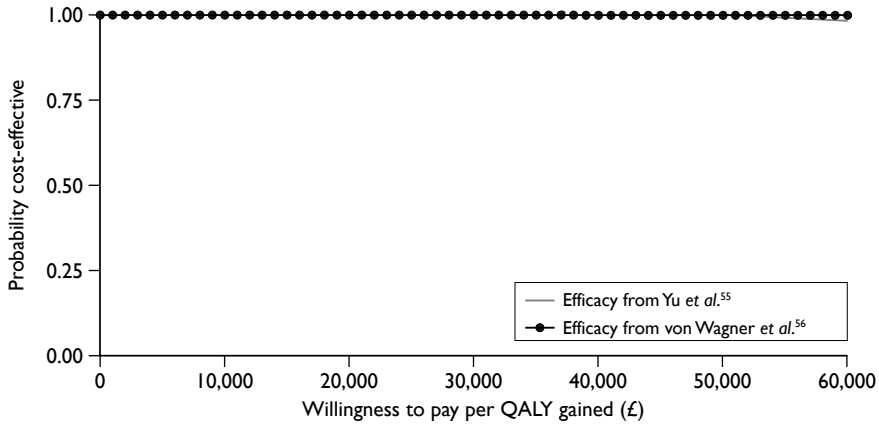

FIGURE 8 Cost-effectiveness acceptability curves for shortened treatment duration with peginterferon alfa-2a and ribavirin combination therapy (16 vs 24 weeks of treatment) for genotypes 2/3.

Peginterferon alfa-2b

Costs and outcomes modelled for genotype 1 patients eligible for shortened duration of treatment on peginterferon alfa-2b and ribavirin combination therapy are presented in *Table 50*.

In the trial reported by Berg and colleagues,[59] shortened treatment duration was associated with a higher SVR than was the case for standard treatment. Shorter duration of treatment is associated with a reduction in total costs of approximately £9000. This is primarily due to the reduction in drug acquisition costs and a reduction in cost of on-treatment monitoring. Given that the SVR is higher for the shorter duration of treatment, there are also small reductions in total cost associated with a reduced risk of disease progression for the cohort of patients receiving shorter duration of treatment. The higher SVR for the shorter duration of treatment also results in improvements in modelled outcomes associated with shorter duration of treatment so that the strategy of shortened treatment duration for this group of patients dominates standard treatment.

Deterministic sensitivity analysis

Table 51 reports the results of a DSA for genotype 1 patients who were eligible for shortened treatment duration with peginterferon alfa-2b and ribavirin combination therapy. The DSAs suggest that the results are generally insensitive to changes in structural assumptions and input parameter values. The greatest variability in ICERs is associated with changes in the mean age of patients at the start of the simulation and the initial distribution of patients across stages of liver disease.

As the included trial by Berg and colleagues[59] gives a potentially counterintuitive result (with shortened treatment duration being more effective than standard duration), we conducted an additional scenario analysis on the impact of the difference in SVR on the cost-effectiveness results, assuming that the SVR for shortened treatment duration is less than or equal to that for standard treatment duration (*Table 52*).

This analysis suggests that shortened treatment duration may be a highly cost-effective option, where there is no difference (or a very small difference) in SVR between shortened and standard treatment duration. Where there is no difference in SVR, shortened duration of treatment dominates standard duration by reducing the utility loss associated with treatment.

TABLE 50 Base-case cost-effectiveness for shortened treatment duration using peginterferon alfa-2b and ribavirin combination therapy in genotype 1 patients

RCT	Treatment duration	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Berg and colleagues[59]	Standard (48 weeks)	26,169	19.74	13.89	
	Shortened (24 weeks)	17,173	20.03	14.38	
	Incremental	–8996	0.29	0.49	Shortened duration dominates

TABLE 51 Deterministic sensitivity analysis for genotype 1 patients eligible for shortened treatment duration using peginterferon alfa-2b and ribavirin combination therapy

	Genotype 1		
	Incremental cost (£)	Incremental QALY	ICER
Base case	–8996	0.49	Shortened duration dominates

continued

TABLE 51 Deterministic sensitivity analysis for genotype 1 patients eligible for shortened treatment duration using peginterferon alfa-2b and ribavirin combination therapy *(continued)*

	Genotype 1		
	Incremental cost (£)	**Incremental QALY**	**ICER**
Structural uncertainty			
Spontaneous SVR from mild (0.002)	–8874	0.47	Shortened duration dominates
Spontaneous SVR from mild (0.010)	–8930	0.48	
Discount cost and outcome at 0%	–12,292	1.15	
Discount cost at 6%, outcome at 1.5%	–7952	0.78	
Baseline cohort characteristics			
Cohort 80% male	–8979	0.49	Shortened duration dominates
Cohort 40% male	–9048	0.51	
Change average age of cohort at start of simulation (base case 40 years old)			
–10 years	–9361	0.60	Shortened duration dominates
+5 years	–8762	0.44	
+10 years	–8495	0.38	
+15 years	–8196	0.33	
Change distribution of cohort across disease stages at start of simulation			
Cohort 100% mild chronic HCV	–7377	0.37	Shortened duration dominates
Cohort 100% moderate HCV	–10,072	0.57	
Cohort 100% CC	–11,711	0.75	
Parameter uncertainty			
Assume SVR is 25% lower in patients with CC	–8848	0.48	Shortened duration dominates
Assume SVR is 50% lower in patients with CC	–8701	0.46	
Cohort 100% CC, assume SVR is 25% lower in patients with CC	–10,233	0.57	
Cohort 100% CC, assume SVR is 50% lower in patients with CC	–8755	0.39	
Transition probability from mild-to-moderate disease	–9198	0.53	
Transition probability from moderate disease to CC	–9426	0.59	
Cost of SVR state = £0	–9041	0.49	
Reduce cost of PEG α-2b by 20%	–8216	0.49	
Reduce cost of PEG α-2b by 30%	–7825	0.49	
Reduce cost of RBV by 20%	–8669	0.49	
Reduce cost of RBV by 20%	–8505	0.49	

CC, compensated cirrhosis; PEG α, peginterferon alfa; RBV, ribavirin.

TABLE 52 Scenario analyses for genotype 1 difference in SVR for shortened treatment duration using peginterferon alfa-2b and ribavirin combination therapy, compared with standard treatment – impact on cost-effectiveness estimates

SVR difference (%)	Incremental cost (£)	Incremental QALY	ICER
0	–5799	0.03	Shortened duration dominates
1	–5587	0.00[a]	6,249,786
3	–5162	–0.06	82,347
5	–4736	–0.12	38,053

a The incremental QALY value of 0.00 appears in the table owing to rounding (to two decimal places). The value here is a very small negative number (–0.0009) hence the positive ICER.

Probabilistic sensitivity analysis

In a PSA, where the probabilities of achieving SVR, health-state costs, health-state utility values, and transition probabilities for the natural history parameters were sampled probabilistically, shortened duration of treatment with peginterferon alfa-2b and ribavirin combination therapy, for genotype 1 patients with baseline LVL and who achieve an RVR, is associated with reduced costs and increased QALYs in all simulations (using efficacy data from Berg and colleagues[59]). *Table 53* reports summary information for the PSAs and *Figure 9* shows the cost-effectiveness plane, including 95% confidence ellipses.

In this analysis of shortened duration of treatment using peginterferon alfa-2b and ribavirin combination therapy for genotype 1 patients, all simulations were in the south-east quadrant of the cost-effectiveness map, where the comparator [in this case standard duration (48 weeks) of treatment] is dominated.

TABLE 53 Mean costs and outcomes (percentile-based 95% CIs) for shortened treatment duration using peginterferon alfa-2b and ribavirin combination therapy from PSA

RCT	Treatment duration	Lifetime costs (£)	QALYs
Berg and colleagues 2009[59]	Standard duration	26,256 (20,507 to 33,463)	13.90 (12.96 to 14.85)
	Shortened duration	17,247 (12,786 to 22,987)	14.38 (13.43 to 15.34)
	Incremental	–9009 (–10,506 to –7717)	0.49 (0.25 to 0.75)

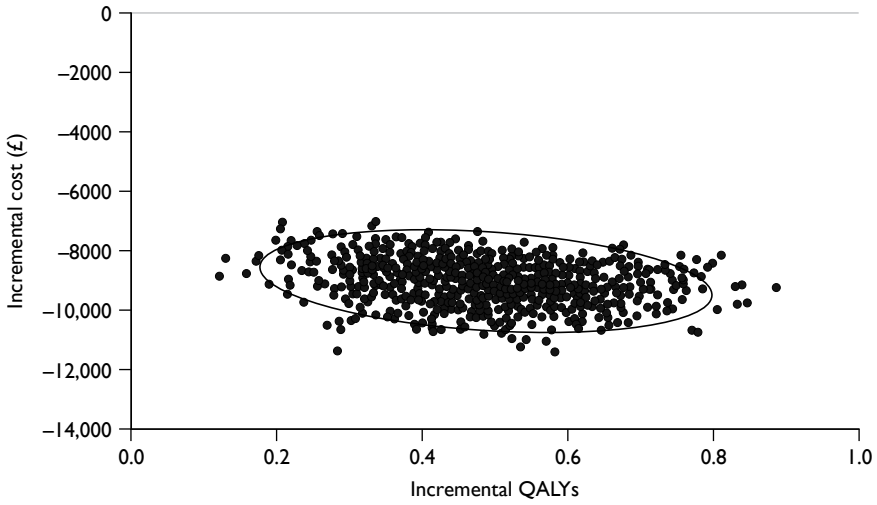

FIGURE 9 Cost-effectiveness plane for genotype 1 patients – incremental cost and incremental quality-adjusted life-years for shortened treatment duration using peginterferon alfa-2b and ribavirin combination therapy (24 vs 48 weeks of treatment) – efficacy from Berg and colleagues.[59]

Re-treated patients

Baseline characteristics (starting age and distribution of patients across stages of chronic liver disease) for re-treated patients in the model are based on those reported for existing patients in the clinical audit at St Mary's Hospital, London,[102] as this group of patients is expected to be older and will probably have more advanced liver disease than would be the case for treatment-naive groups.

Peginterferon alfa-2a

Sustained virological responses for this patient population are taken from the RCT reported by Jensen and colleagues,[88] which compared re-treatment with varying doses and duration of peginterferon alfa-2a in patients who had previously failed to respond to, or relapsed on, peginterferon or non-peginterferon alfa plus ribavirin. This trial was not included in our systematic review of clinical effectiveness, which specified, in line with the scope issued by NICE, that the comparator in trials of re-treated patients should be BSC (i.e. excluding active treatment with interferon alfa). For this analysis, in the absence of any relevant trial data, we assumed that the SVR for the cohort of re-treated patients receiving BSC would be zero. The assumed treatment duration for genotype 1 patients is 72 weeks, based on the SPC for peginterferon alfa-2a.[42] For genotype non-1 patients the treatment duration is 48 weeks (see *Appendix 8*).

Costs and outcomes modelled for re-treatment in patients previously treated with peginterferon alfa-2a and ribavirin combination therapy are presented in *Table 54*. This table reports total costs (antiviral treatment and supportive care), health outcomes (in terms of life-years and QALYs) and the incremental cost-per-QALYs ratios.

The impact of re-treating this group of patients is to improve the predicted outcome (by 0.31 and 0.59 QALYs for genotype 1 and genotype non-1, respectively) and to increase lifetime costs (by £16,130 and £6419 QALYs for genotype 1 and genotype non-1, respectively). The reduction in supportive care costs associated with disease progression in both groups of patients (genotype 1 and genotype non-1) is insufficient to fully offset the additional costs of antiviral treatment.

The cost-effectiveness results in *Table 54* do not take account of patients withdrawing from treatment owing to adverse events, nor do they consider the impact of treatment stopping rules (e.g. ceasing treatment at 12 weeks in patients who do not demonstrate an EVR). *Table 55* reports cost-effectiveness results for re-treated patients, allowing for patient withdrawals owing to adverse effects of treatment with peginterferon alfa and ribavirin combination therapy. This has

TABLE 54 Base-case cost-effectiveness for re-treatment using peginterferon alfa-2a and ribavirin combination therapy in previously treated patients

Re-treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotype 1				
BSC	26,221	16.75	10.74	
PEG α-2a	42,350	17.07	11.05	
Incremental	16,130	0.33	0.31	52,587
Genotype non-1				
BSC	26,221	16.75	10.74	
PEG α-2a	32,640	17.28	11.33	
Incremental	6419	0.54	0.59	10,926

PEG α, peginterferon alfa.

a marginal impact on the cost-effectiveness results, with the ICER for patients with genotype 1 remaining high.

Table 56 reports cost-effectiveness results for re-treated patients, allowing for the adoption of early stopping rules whereby patients who do not demonstrate an EVR stop treatment at 12 weeks. This has a substantial impact on the cost-effectiveness results, reducing the increase in total costs for patients treated with peginterferon alfa and ribavirin combination therapy to between £1415 and £3398, depending on genotype grouping, while also increasing the QALY gain by approximately 0.06 QALYs. As a result the ICER for patients with genotype 1 falls to £9169.

The EVRs used in the analysis reported in *Table 56* are taken from the Roche submission to NICE,[104] as Jensen and colleagues[88] do not report EVR separately for the genotype groupings used in this analysis. The interpretation of the data available in the MS is difficult, as the number of patients achieving SVR is not reported according to whether patients demonstrated an EVR, for each treatment arm. Rather, the submission reports only predictive values for patients achieving full viral suppression at week 12. The analysis in *Table 56* assumes that all patients who achieve an SVR demonstrated an EVR.

TABLE 55 Cost-effectiveness of re-treatment using peginterferon alfa-2a and ribavirin combination therapy in previously treated patients – allowing for patients withdrawing from treatment owing to adverse events

Re-treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotype 1				
BSC	26,221	16.75	10.74	
PEG α-2a	41,900	17.07	11.05	
Incremental	15,680	0.33	0.31	50,730
Genotype non-1				
BSC	26,221	16.75	10.74	
PEG α-2a	32,488	17.28	11.33	
Incremental	6267	0.54	0.59	10,650

PEG α, peginterferon alfa.

TABLE 56 Cost-effectiveness of re-treatment using peginterferon alfa-2a and ribavirin combination therapy in previously treated patients – applying early stopping rule for patients not demonstrating an EVR

Re-treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotype 1				
BSC	26,221	16.75	10.74	
PEG α-2a	29,619	17.07	11.11	
Incremental	3398	0.33	0.37	9169
Genotype non-1				
BSC	26,221	16.75	10.74	
PEG α-2a	27,636	17.28	11.36	
Incremental	1415	0.54	0.62	2294

PEG α, peginterferon alfa.

Deterministic sensitivity analysis

Table 57 reports the results of a DSA for re-treatment using peginterferon alfa-2a and ribavirin combination therapy in previously treated patients. These are predominantly univariate sensitivity analyses, varying one parameter at a time from its base-case value, leaving all other variables unchanged.

TABLE 57 Deterministic sensitivity analysis for re-treatment using peginterferon alfa-2a and ribavirin combination therapy in previously treated patients – applying early stopping rule for patients not demonstrating an EVR

	Genotype 1			Genotype non-1		
	Incremental cost (£)	Incremental QALY	ICER	Incremental cost (£)	Incremental QALY	ICER
Base case	3398	0.37	9169	1415	0.62	2294
Structural uncertainty						
Spontaneous SVR from mild (0.002)	3460	0.36	9685	1516	0.60	2547
Spontaneous SVR from mild (0.010)	3431	0.36	9442	1469	0.61	2428
Discount cost and outcome at 0%	945	0.84	1121	–2588	1.39	–1864
Discount cost at 6%, outcome at 1.5%	4270	0.58	7355	2838	0.96	2957
Baseline cohort characteristics						
Cohort 80% male	3414	0.37	9306	1441	0.61	2360
Cohort 40% male	3348	0.38	8754	1334	0.64	2097
Change average age of cohort at start of simulation (base case 40 years old)						
–10 years	3052	0.47	6500	851	0.78	1093
+5 years	3624	0.32	11,401	1784	0.53	3361
+10 years	3887	0.26	14,685	2213	0.44	4983
+15 years	4188	0.21	19,740	2705	0.36	7547
Change distribution of cohort across disease stages at start of simulation						
Cohort 100% mild chronic HCV	5325	0.23	23,560	4560	0.38	11,970
Cohort 100% moderate HCV	3152	0.37	8508	1014	0.62	1644
Cohort 100% CC	1680	0.52	3232	–1389	0.86	–1614
Parameter uncertainty						
Assume SVR is 25% lower in patients with CC	3784	0.33	11,573	2045	0.55	3747
Assume SVR is 50% lower in patients with CC	4170	0.28	14,720	2675	0.47	5638
Cohort 100% CC, assume SVR is 25% lower in patients with CC	2886	0.38	7526	579	0.64	907
Cohort 100% CC, assume SVR is 50% lower in patients with CC	4091	0.25	16,570	2546	0.42	6135
Transition probability from mild-to-moderate disease = 0.04	3288	0.39	8462	1236	0.65	1912
Transition probability from moderate disease to CC = 0.073	3126	0.43	7313	971	0.71	1368
Cost of SVR state = £0	3360	0.37	9066	1353	0.62	2193
Reduce cost of PEG α-2a by 20%	2868	0.37	7739	796	0.62	1290
Reduce cost of PEG α-2a by 30%	2603	0.37	7024	486	0.62	787
Reduce cost of RBV by 20%	2316	0.37	6248	1054	0.62	1708
Reduce cost of RBV by 20%	2161	0.37	5831	873	0.62	1415

CC, compensated cirrhosis; PEG α, peginterferon alfa; RBV, ribavirin.

The DSA suggests that the results are robust to a change in structural assumptions (allowing spontaneous SVR from the mild chronic HCV state), the proportion of the baseline cohort that is male and variation in early disease transition probabilities. Reducing drug acquisition costs has the effect of improving the cost-effectiveness of re-treatment, as would be expected, by reducing incremental costs while leaving incremental outcome unchanged.

The results are highly sensitive to two assumptions regarding baseline cohort characteristics. Increasing age at entry to the model is associated with a substantial increase in the ICER – the ICER value approximately doubles if age at entry is increased by 15 years from the base case. This arises as the QALY gain from re-treatment is reduced by approximately 43%, while incremental cost increases by 23%, for genotype 1 patients. The results also appear to be sensitive to the distribution of patients across liver disease stages, at entry to the model. Higher QALY gains are associated with more advanced disease stage, with lower incremental costs; however, in this analysis we have assumed the same SVR in patients with and without cirrhosis. Subsequent analyses suggest that the ICER is also sensitive to variation in the SVR applied for patients with cirrhosis at baseline.

Probabilistic sensitivity analysis

In a PSA where the probabilities of achieving EVR and SVR, health-state costs, health-state utility values and transition probabilities for the natural history parameters were sampled probabilistically, re-treatment using peginterferon alfa-2a and ribavirin combination therapy is associated with increased QALYs (with a range from 0.05 to 0.59 QALYs for genotype 1 patients, and from 0.05 to 2.94 QALYs for genotype non-1 patients), but for genotype 1 patients is typically also associated with increased costs when compared with BSC. *Table 58* provides summary information and *Figures 10* and *11* scatter plots that also show the 95% confidence ellipses. The incremental cost was negative in approximately 25% of simulations for genotype non-1 patients.

TABLE 58 Mean costs and outcomes (percentile-based 95% CIs) for re-treatment using peginterferon alfa-2a and ribavirin combination therapy, from PSA

Re-treatment	Lifetime costs (£)	QALYs
Genotype 1		
BSC	26,183 (17,678 to 35,971)	10.79 (9.89 to 11.73)
PEG α-2a	29,552 (22,032 to 38,284)	11.15 (10.27 to 12.02)
Incremental	3369 (1573 to 4509)	0.37 (0.13 to 0.67)
Genotype non-1		
BSC	26,005 (17,302 to 36,253)	10.81 (9.91 to 11.74)
PEG α-2a	27,186 (19,864 to 36,507)	11.44 (10.41 to 12.51)
Incremental	1,181 (–4127 to 4030)	0.63 (0.14 to 1.49)

PEG α, peginterferon alfa.

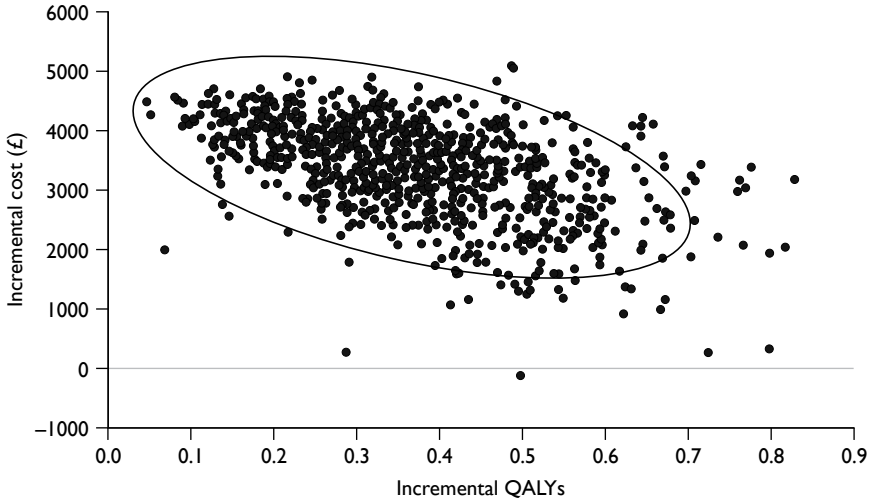

FIGURE 10 Cost-effectiveness plane for genotype 1 – incremental cost and incremental QALYs for re-treatment using peginterferon alfa-2a and ribavirin combination therapy (applying early stopping rule based on early virological response).

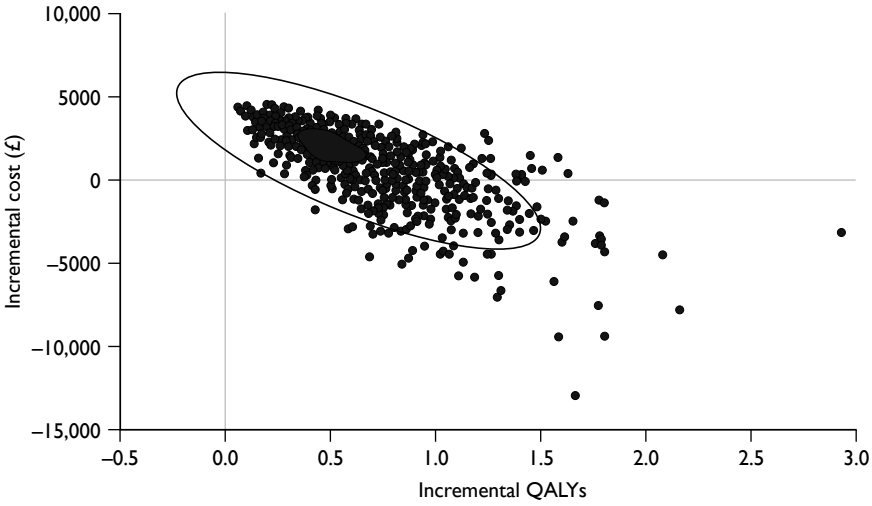

FIGURE 11 Cost-effectiveness plane for genotype non-1 – incremental cost and incremental QALYs for re-treatment using peginterferon alfa-2a and ribavirin combination therapy (applying early stopping rule based on early virological response).

In this analysis, re-treatment using peginterferon alfa and ribavirin combination therapy for genotype 1 patients has a probability of being cost-effective (compared with BSC) of 90% at a willingness-to-pay threshold of £20,000 per QALY and 98% at a willingness-to-pay threshold of £30,000 if a stopping rule based on EVR is adopted. If patients are treated for the full 72 weeks, regardless of EVR, the equivalent figures are 2% and 11% (*Figure 12*). For genotype non-1 patients, the probability of re-treatment using peginterferon alfa plus ribavirin being cost-effective (compared with BSC) was 96% at a willingness-to-pay threshold of £20,000 per QALY and 98% at a willingness-to-pay threshold of £30,000, when adopting the stopping rule based on EVR (*Figure 13*).

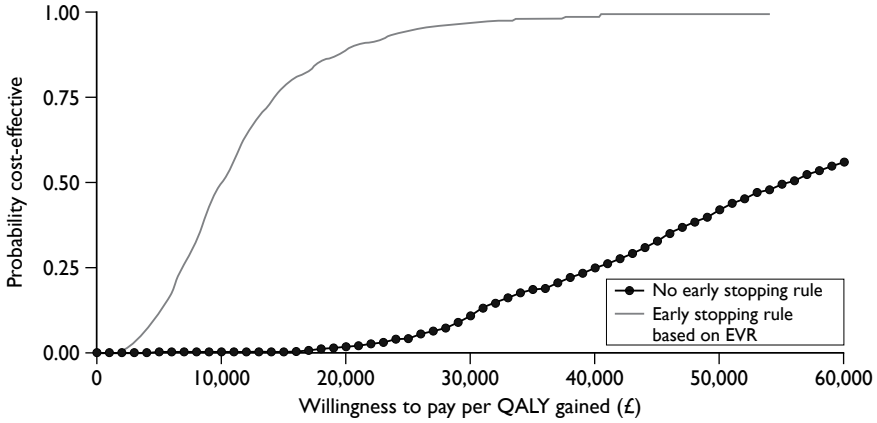

FIGURE 12 Cost-effectiveness acceptability curves for re-treatment of genotype 1 patients with peginterferon alfa-2a, with and without stopping rules based on EVR.

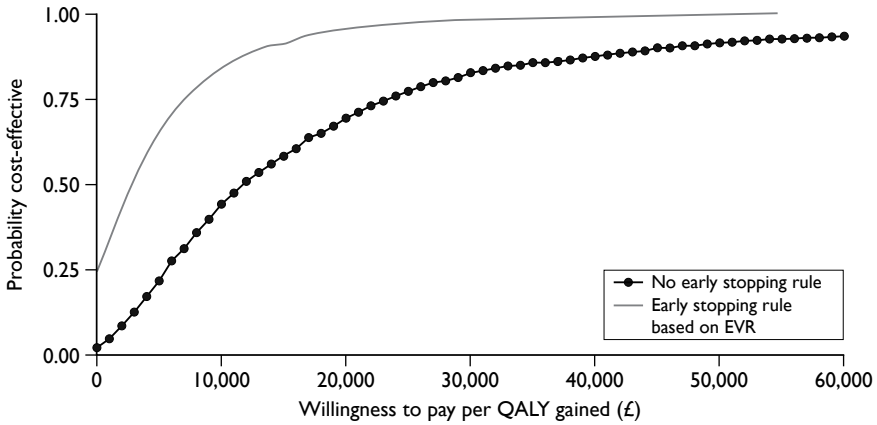

FIGURE 13 Cost-effectiveness acceptability curves for re-treatment of genotype non-1 patients with peginterferon alfa-2a, with and without stopping rules based on EVR.

Peginterferon alfa-2b

Sustained virological responses for this patient population are taken from the MS by Schering-Plough, which reported treatment outcomes for the EPIC3 study[96] (a multicentre, non-randomised open-label uncontrolled study). This study did not meet the inclusion criteria for our systematic review of clinical effectiveness (see *Appendix 8* for an explanation of the choice of clinical evidence in this patient group). The assumed treatment duration for all patients is 48 weeks, and the SVR for the cohort of patients receiving BSC is assumed to be zero.

Costs and outcomes modelled for re-treatment in patients previously treated with peginterferon alfa-2b and ribavirin combination therapy are presented in *Table 59*. This table reports total costs (antiviral treatment and supportive care), health outcomes (in terms of life-years and QALYs) and the incremental cost-per-QALY ratios.

The impact of re-treating this group of patients is to improve the predicted outcome (by 0.39 and 1.72 QALYs for genotypes 1 and 4 and genotypes 2 and 3, respectively) and to increase lifetime costs (by £9380 for genotypes 1 and 4). The reduction in supportive care costs associated with disease progression in genotype 2 + 3 patients, associated with re-treatment with peginterferon alfa-2b and ribavirin combination therapy, is sufficient to fully offset the additional costs of antiviral treatment. This is due to the high SVR reported for genotype 2 + 3 patients (58.3% overall and 56.8% in those demonstrating an EVR) reported for the EPIC3 study,[96] in the MS.

The cost-effectiveness results in *Table 59* do not take account of patients withdrawing from treatment owing to adverse events or consider the impact of treatment stopping rules (e.g. ceasing treatment at 12 weeks in patients who do not demonstrate an EVR). *Table 60* reports cost-effectiveness results for re-treated patients, allowing for patient withdrawals owing to adverse effects of treatment with peginterferon alfa-2b and ribavirin combination therapy; this has a marginal impact on the cost-effectiveness results.

Table 61 reports cost-effectiveness results for re-treated patients, allowing for the adoption of early stopping rules whereby patients who do not demonstrate an EVR stop treatment at 12 weeks. This has a substantial impact on the cost-effectiveness results, reducing the increase in total costs for genotype 1 and 4 patients treated with peginterferon alfa-2b and ribavirin combination therapy to £3256. As a result the ICER for patients with genotype 1 falls to £7681.

TABLE 59 Base-case cost-effectiveness for re-treatment using peginterferon alfa-2b and ribavirin combination therapy in previously treated patients

Re-treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotypes 1 + 4				
BSC	26,221	16.75	10.74	
PEG α-2b	35,601	17.12	11.14	
Incremental	9380	0.37	0.39	23,912
Genotypes 2 + 3				
BSC	26,221	16.75	10.74	
PEG α-2b	25,232	18.21	12.46	
Incremental	–989	1.47	1.72	PEG α-2b dominates

PEG α, peginterferon alfa.

TABLE 60 Cost-effectiveness of re-treatment using peginterferon alfa-2b and ribavirin combination therapy in previously treated patients – allowing for patients withdrawing from treatment owing to adverse events

Re-treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotypes 1 + 4				
BSC	26,221	16.75	10.74	
PEG α-2b	35,417	17.12	11.14	
Incremental	9197	0.37	0.39	23,384
Genotypes 2 + 3				
BSC	26,221	16.75	10.74	
PEG α-2b	25,048	18.21	12.46	
Incremental	–1173	1.47	1.72	PEG α-2b dominates

PEG α, peginterferon alfa.

TABLE 61 Cost-effectiveness of re-treatment using peginterferon alfa-2b and ribavirin combination therapy in previously treated patients – applying early stopping rule for patients not demonstrating an EVR

Re-treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotypes 1 + 4				
BSC	26,221	16.75	10.74	
PEG α-2b	29,476	17.12	11.17	
Incremental	3256	0.37	0.42	7681
Genotypes 2 + 3				
BSC	26,221	16.75	10.74	
PEG α-2b	23,371	18.21	12.47	
Incremental	–2850	1.47	1.73	PEG α-2b dominates

PEG α, peginterferon alfa.

Deterministic sensitivity analysis

Table 62 reports the results of a DSA for re-treatment using peginterferon alfa-2b and ribavirin combination therapy in previously treated patients. These are predominantly univariate sensitivity analyses – that is, varying one parameter at a time, from its base-case value, leaving all of the other variables unchanged. The DSA suggests that the results are robust to a change in structural assumptions (allowing spontaneous SVR from the mild chronic HCV state), the proportion of the baseline cohort that is male and transition probabilities for early disease states. Reducing drug acquisition costs has the effect of reducing the ICER, as might be expected, as it reduces the drug costs while the outcome difference is unchanged.

The greatest variability in ICERs is associated with changes in the age at which patients enter the model, the distribution of patients across disease stages and (to a lesser extent) response to treatment (SVR) for patients with cirrhosis. Increasing the mean age of patients at the start of the simulation up to 15 years leads to an approximate doubling of the ICER for genotype 1 and 4 patients and results in a positive, though low-value, ICER for genotype 2 and 3 patients. In both cases, the QALY gain with treatment is approximately halved. Similarly, alternative assumptions regarding the stage of liver disease in which patients enter the model has a large impact on the ICER, with less favourable results associated with patients being in the earlier (lower fibrosis) stages of disease. For genotype 2 and 3 patients the ICER becomes positive if all patients in the modelled cohorts have mild chronic HCV (rather than moderate chronic HCV or compensated cirrhosis).

TABLE 62 Deterministic sensitivity analysis for re-treatment using peginterferon alfa-2b and ribavirin combination therapy in previously treated patients – applying early stopping rule for patients not demonstrating an EVR

	Genotypes 1 + 4			Genotypes 2 + 3		
	Incremental cost (£)	Incremental QALY	ICER	Incremental cost (£)	Incremental QALY	ICER
Base case	3256	0.42	7681	–2850	1.73	–1650
Structural uncertainty						
Spontaneous SVR from mild (0.002)	3326	0.41	8,139	–2575	1.67	–1545
Spontaneous SVR from mild (0.010)	3294	0.42	7923	–2702	1.69	–1594
Discount cost and outcome at 0%	460	0.96	477	–13,840	3.84	–3600
Discount cost at 6%, outcome at 1.5%	4250	0.66	6408	1055	2.67	396
Baseline cohort characteristics						
Cohort 80% male	3274	0.42	7802	–2778	1.71	–1624
Cohort 40% male	3199	0.44	7313	–3073	1.78	–1726
Change average age of cohort at start of simulation (base case 40 years old)						
–10 years	2862	0.54	5331	–4399	2.17	–2027
+5 years	3514	0.36	9658	–1837	1.49	–1232
+10 years	3813	0.30	12,579	–660	1.25	–527
+15 years	4156	0.24	17,087	690	1.02	678
Change distribution of cohort across disease stages at start of simulation						
Cohort 100% mild chronic HCV	5453	0.26	21,048	5783	1.08	5359
Cohort 100% moderate HCV	2976	0.42	7022	–3951	1.73	–2289
Cohort 100% CC	1297	0.59	2184	–10,548	2.40	–4402
Parameter uncertainty						
Assume SVR is 25% lower in patients with CC	3696	0.37	9878	–1121	1.53	–732
Assume SVR is 50% lower in patients with CC	4136	0.32	12,751	607	1.34	455
Cohort 100% CC, assume SVR is 25% lower in patients with CC	2672	0.44	6093	–5146	1.78	–2884
Cohort 100% CC, assume SVR is 50% lower in patients with CC	4046	0.28	14,304	255	1.17	218
Transition probability from mild-to-moderate disease = 0.04	3131	0.44	7044	–3342	1.81	–1849
Transition probability from moderate disease to CC = 0.073	2946	0.49	6028	–4069	1.98	–2053
Cost of SVR state = £0	3213	0.42	7578	–3020	1.73	–1749
Reduce cost of PEG α-2b by 20%	2518	0.42	5940	–4161	1.73	–2409
Reduce cost of PEG α-2b by 30%	2149	0.42	5069	–4816	1.73	–2789
Reduce cost of RBV by 20%	2946	0.42	6950	–3400	1.73	–1969
Reduce cost of RBV by 20%	2791	0.42	6584	–3675	1.73	–2128

CC, compensated cirrhosis; PEG α, peginterferon alfa; RBV, ribavirin.

Probabilistic sensitivity analysis

In a PSA, where the probabilities of achieving EVR and SVR, health-state costs, health-state utility values, and transition probabilities for the natural history parameters were sampled probabilistically, re-treatment using peginterferon alfa and ribavirin combination therapy is associated with increased QALYs (with a range from 0.08 to 0.80 QALYs for genotypes 1 and 4 and from 0.28 to 3.06 QALYs for patients with genotypes 2 and 3), but for genotype 1 and 4 patients is typically also associated with increased costs when compared with BSC (*Table 63* provides summary information and *Figures 14* and *15* scatter plots, which also show the 95% confidence ellipses). The incremental cost was negative in approximately 84% of simulations for genotype 2 and 3 patients.

In this analysis, re-treatment using peginterferon alfa-2b and ribavirin combination therapy for genotype 1 and 4 patients had a probability of being cost-effective (compared with BSC) of 99% at a willingness-to-pay threshold of £20,000 per QALY, and 100% at a willingness-to-pay

TABLE 63 Mean costs and outcomes (percentile-based 95% CIs) for re-treatment using peginterferon alfa-2b and ribavirin combination therapy, from PSA

Re-treatment	Lifetime costs (£)	QALYs
Genotypes 1 + 4		
BSC	25,820 (17,909 to 35,424)	10.78 (9.86 to 11.72)
PEG α-2b	29,118 (22,213 to 37,485)	11.20 (10.38 to 12.01)
Incremental	3298 (1785 to 4480)	0.42 (0.22 to 0.66)
Genotypes 2 + 3		
BSC	25,914 (17,928 to 35,721)	10.78 (9.89 to 11.69)
PEG α-2b	23,250 (19,240 to 28,246)	12.48 (11.65 to 13.32)
Incremental	–2664 (–8971 to 1846)	1.69 (0.88 to 2.48)

PEG α, peginterferon alfa.

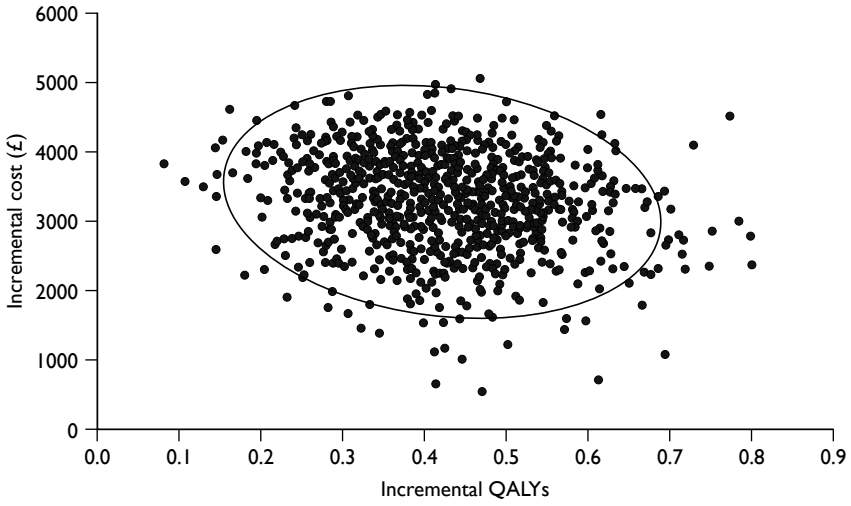

FIGURE 14 Cost-effectiveness plane for genotypes 1 and 4 – incremental cost and incremental QALYs for re-treatment using peginterferon alfa-2b and ribavirin combination therapy (applying early stopping rule based on EVR).

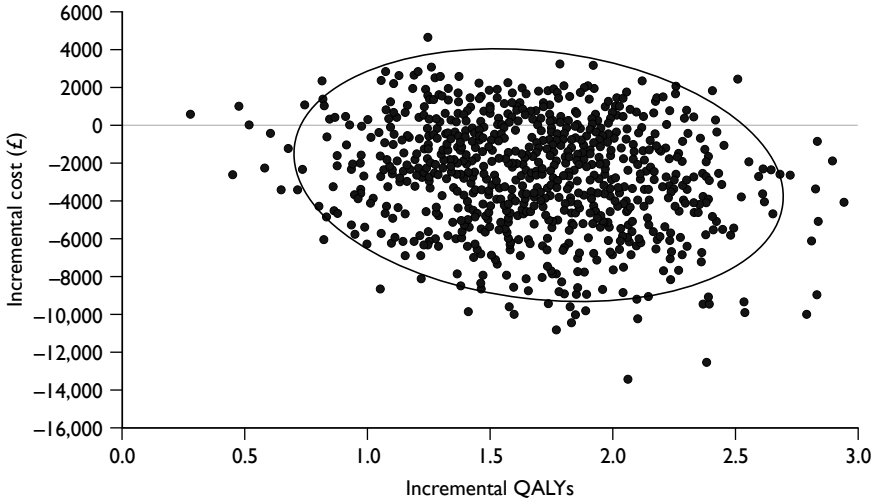

FIGURE 15 Cost-effectiveness plane for genotypes 2 and 3 – incremental cost and incremental QALYs for re-treatment using peginterferon alfa-2b and ribavirin combination therapy (applying early stopping rule based on EVR).

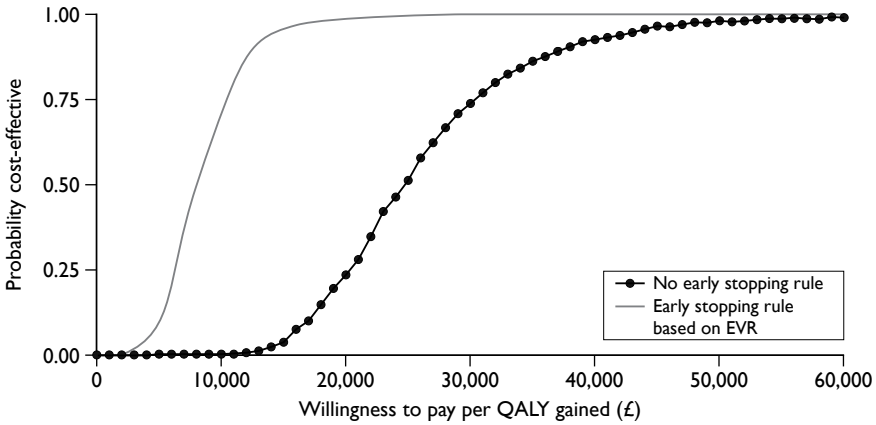

FIGURE 16 Cost-effectiveness acceptability curves for re-treatment of genotype 1 and 4 patients with peginterferon alfa-2b, with and without stopping rules based on EVR.

threshold of £30,000 if a stopping rule based on EVR is adopted. If patients are treated for the full 48 weeks, regardless of EVR, the equivalent figures are 24% and 74% (*Figure 16*). For genotype 2 and 3 patients the probability of re-treatment using peginterferon alfa-2b and ribavirin being cost-effective (compared with BSC) was 100% at a willingness-to-pay threshold of £20,000 per QALY, and at a willingness-to-pay threshold of £30,000 when adopting the stopping rule based on EVR (*Figure 17*).

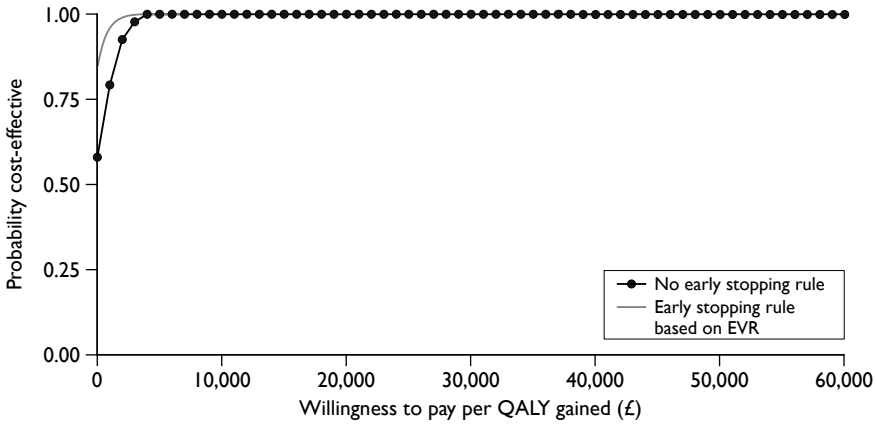

FIGURE 17 Cost-effectiveness acceptability curves for re-treatment of genotype 2 and 3 patients with peginterferon alfa-2b, with and without stopping rules based on EVR.

HCV/HIV co-infected patients

No data reporting the distribution of treatment-eligible HCV/HIV co-infected patients across liver disease stages were identified in our searches. The distribution of HCV/HIV co-infected patients across stages of chronic liver disease, at entry to the model, is based on that reported for new mono-infected patients in the clinical audit at St Mary's Hospital.[102] SVRs for this patient population are based on those reported in two recent systematic reviews of antiviral treatment with peginterferon alfa in HCV/HIV co-infected patients, which included trials with active treatment comparators[50,51] (see *Appendix 9*). The systematic review of clinical effectiveness in this report (see *Chapter 4*) specified, in line with the scope issued by NICE, that the comparator in trials of HCV/HIV co-infected patients should be BSC (excluding active treatment with interferon alfa). For this analysis, in the absence of any relevant trial data, we assumed that the SVR for the cohort of re-treated patients receiving BSC would be zero.

The tables in this section report lifetime costs (antiviral treatment and BSC), health outcomes (in terms of life-years and QALYs) and the incremental cost-per-QALY ratios. The assumed treatment duration for all patients in the base case is 48 weeks, regardless of genotype. This is in accordance with the SPC for peginterferon alfa-2a[42] and for peginterferon alfa-2b.[42]

Peginterferon alfa-2a

Costs and outcomes modelled for patients co-infected with HCV/HIV receiving combination therapy with peginterferon alfa-2a plus ribavirin are presented in *Table 64*.

The impact of treating this group is to improve the predicted outcome (by 0.75 and 1.86 QALYs for genotypes 1 and 4 and genotypes 2 and 3, respectively) and to increase lifetime costs for patients with genotypes 1 and 4 (by £5932). However, in patients with genotypes 2 and 3 the modelled reduction in supportive care costs (in the peginterferon-treated cohort) offsets the additional costs of antiviral treatment; in this situation the strategy of providing antiviral treatment dominates.

The cost-effectiveness results in *Table 64* do not take account of uncertainties regarding the potential impact of HIV co-infection on the natural history of HCV infection, overall mortality, utility gains from successful treatment or additional costs of on-treatment monitoring.

A published meta-analysis[25] suggests that a RR for cirrhosis of 2.07 (95% CI 1.4 to 3.07) and a RR for decompensation of 6.14 (95% CI 2.86 to 13.20) in HCV/HIV co-infected patients compared with that in HCV mono-infected patients. *Table 65* reports the cost-effectiveness results from the model when these RRs for liver disease progression are applied to the baseline risks in the natural history model. This suggests that treatment using peginterferon alfa-2a and ribavirin combination therapy will be more cost-effective in HCV/HIV co-infected patients, if the risks of fibrosis progression are greater than for mono-infected patients.

Table 66 reports the cost-effectiveness results from the model when the age-specific mortality risks are doubled for HCV/HIV co-infected patients. This would result in an age-specific life

TABLE 64 Base-case cost-effectiveness for treatment of HCV/HIV co-infected patients with peginterferon alfa-2a and ribavirin combination therapy

Genotype	Treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	PEG α-2a	28,133	19.43	13.40	
	Incremental	5932	0.51	0.75	7941
Genotypes 2 + 3	BSC	22,201	18.93	12.65	
	PEG α-2a	20,484	20.13	14.51	
	Incremental	–1717	1.20	1.86	PEG α-2a dominates

PEG α, peginterferon alfa.

TABLE 65 Cost-effectiveness of treatment of HCV/HIV co-infected patients with peginterferon alfa-2a and ribavirin combination therapy – using higher fibrosis progression probability for co-infected patients

Genotype	Treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotypes 1 + 4	BSC	31,839	16.91	10.90	
	PEG α-2a	35,254	17.94	12.10	
	Incremental	3415	1.03	1.21	2833
Genotypes 2 + 3	BSC	31,839	16.91	10.90	
	PEG α-2a	24,137	19.37	13.84	
	Incremental	–7703	2.46	2.95	PEG α-2a dominates

PEG α, peginterferon alfa.

TABLE 66 Cost-effectiveness of treatment of HCV/HIV co-infected patients with peginterferon alfa-2a and ribavirin combination therapy – higher age-specific mortality risks for co-infected patients

Genotype	Treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotypes 1 + 4	BSC	19,865	17.46	11.70	
	PEG α-2a	26,398	17.84	12.31	
	Incremental	6534	0.38	0.61	10,704
Genotypes 2 + 3	BSC	19,865	17.46	11.70	
	PEG α-2a	19,578	18.36	13.23	
	Incremental	–287	0.91	1.53	PEG α-2a dominates

PEG α, peginterferon alfa.

expectancy of 33.2 years at the age of 40 years for an HIV infected person (in the absence of chronic liver disease) compared with 39.8 years if the age-specific mortality risks for the general population are applied (as in the base-case analysis). This reduces lifetime costs and QALYs both for peginterferon treated and BSC cohorts. This suggests that treatment using peginterferon alfa-2a and ribavirin combination therapy will be less cost-effective in HCV/HIV co-infected patients, if mortality risk is greater than for mono-infected patients. However, while the incremental cost for peginterferon treatment increases and the QALY gain is reduced, with higher mortality risk for HCV/HIV co-infected patients, treatment with peginterferon still dominates BSC for genotype 2 and 3 patients.

Tables 67 and *68* report cost-effectiveness results from alternative assumptions on the utility gain for HCV/HIV co-infected patients who achieve an SVR. In the first case, the utility gain is assumed to be one-half of that reported for HCV mono-infected patients, and in the second case the utility gain is assumed to be zero. In both cases the QALY gain from treatment with peginterferon is reduced, indicating that treatment using peginterferon alfa-2a and ribavirin combination therapy will be less cost-effective in HCV/HIV co-infected patients, if utility gain from SVR is lower in HCV/HIV co-infected patients than in mono-infected patients.

A final scenario analysis was performed to consider the impact of on-treatment monitoring costs on the cost-effectiveness of antiviral treatment for HCV/HIV co-infected patients. *Table 69* reports the cost-effectiveness results from the model if on-treatment costs for HCV/HIV co-infected patients are assumed to be double those for HCV mono-infected patients. As with the previous analyses, this assumption suggests that treatment using peginterferon alfa-2a and ribavirin combination therapy is less cost-effective than in the base-case analysis. However, treatment with peginterferon still dominates BSC for genotype 2 and 3 patients.

TABLE 67 Cost-effectiveness of treatment of HCV/HIV co-infected patients with peginterferon alfa-2a and ribavirin combination therapy – reduce utility gain for SVR by half

Genotype	Treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	PEG α-2a	28,133	19.43	13.25	
	Incremental	5932	0.51	0.60	9889
Genotypes 2 + 3	BSC	22,201	18.93	12.65	
	PEG α-2a	20,484	20.13	14.16	
	Incremental	–1717	1.20	1.51	PEG α-2a dominates

PEG α, peginterferon alfa.

TABLE 68 Cost-effectiveness of treatment of HCV/HIV co-infected patients with peginterferon alfa-2a and ribavirin combination therapy – no utility gain for patients achieving SVR

Genotype	Treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	PEG α-2a	28,133	19.43	13.10	
	Incremental	5932	0.51	0.45	13,103
Genotypes 2 + 3	BSC	22,201	18.93	12.65	
	PEG α-2a	20,484	20.13	13.81	
	Incremental	–1717	1.20	1.16	PEG α-2a dominates

PEG α, peginterferon alfa.

TABLE 69 Cost-effectiveness of treatment of HCV/HIV co-infected patients with peginterferon alfa-2a and ribavirin combination therapy – higher on-treatment monitoring costs for co-infected patients

Genotype	Treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	PEG α-2a	29,184	19.43	13.40	
	Incremental	6983	0.51	0.75	9348
Genotypes 2 + 3	BSC	22,201	18.93	12.65	
	PEG α-2a	21,535	20.13	14.51	
	Incremental	–666	1.20	1.86	PEG α-2a dominates

PEG α, peginterferon alfa.

Deterministic sensitivity analysis

Table 70 reports the results of a DSA for treatment of HCV/HIV co-infected patients using peginterferon alfa-2a and ribavirin combination therapy. These suggest that the results are robust to a change in structural assumptions (allowing spontaneous SVR from the mild chronic HCV state), the proportion of the baseline cohort that is male, transition probabilities for early disease states and cost of the SVR health state. Reducing drug acquisition costs has the effect of reducing the ICER, as might be expected, as it reduces the drug costs while the outcome difference is unchanged.

TABLE 70 Deterministic sensitivity analysis for treatment of HCV/HIV co-infected patients with peginterferon alfa-2a and ribavirin combination therapy

	Genotype 1			Genotypes 2 + 3		
	Incremental cost (£)	Incremental QALY	ICER	Incremental cost (£)	Incremental QALY	ICER
Base case	5932	0.75	7941	–1717	1.86	–924
Structural uncertainty						
Spontaneous SVR from mild (0.002)	6144	0.70	8765	–1213	1.75	–693
Spontaneous SVR from mild (0.010)	6047	0.72	8374	–1445	1.80	–803
Discount cost and outcome at 0%	206	1.88	109	–15,331	4.56	–3360
Discount cost at 6%, outcome at 1.5%	7745	1.24	6266	2593	3.02	858
Baseline cohort characteristics						
Cohort 80% male	5961	0.74	8055	–1648	1.84	–895
Cohort 40% male	5842	0.77	7598	–1933	1.91	–1012
Change average age of cohort at start of simulation (base case 40 years old)						
–10 years	5299	0.93	5722	–3223	2.28	–1411
+5 years	6338	0.65	9734	–752	1.63	–461
+10 years	6804	0.55	12,291	354	1.40	253
+15 years	7323	0.46	16,029	1588	1.17	1359
Change distribution of cohort across disease stages at start of simulation						
Cohort 100% mild chronic HCV	8744	0.53	16,524	4969	1.34	3706
Cohort 100% moderate HCV	4064	0.87	4655	–6159	2.16	–2854
Cohort 100% CC	1217	1.19	1018	–12,928	2.92	–4423
Parameter uncertainty						
Assume SVR is 25% lower in patients with CC	6189	0.72	8648	–1107	1.78	–620
Assume SVR is 50% lower in patients with CC	6446	0.68	9420	–496	1.71	–290
Cohort 100% CC, assume SVR is 25% lower in patients with CC	3784	0.88	4295	–6825	2.18	–3135
Cohort 100% CC, assume SVR is 50% lower in patients with CC	6351	0.57	11,194	–721	1.43	–504
Transition probability from mild-to-moderate disease = 0.04	5581	0.81	6916	–2552	2.00	–1275
Transition probability from moderate disease to CC = 0.073	5186	0.92	5642	–3492	2.27	–1540
Cost of SVR state = £0	5854	0.75	7836	–1904	1.86	–1024
Reduce cost of PEG α-2a by 20%	4714	0.75	6310	–2935	1.86	–1579
Reduce cost of PEG α-2a by 30%	4105	0.75	5495	–3545	1.86	–1907
Reduce cost of RBV by 20%	5221	0.75	6989	–2428	1.86	–1306
Reduce cost of RBV by 20%	4866	0.75	6513	–2784	1.86	–1498

CC, compensated cirrhosis; PEG α, peginterferon alfa; RBV, ribavirin.

The greatest variability in ICERs is associated with changes in the age at which patients enter the model, the distribution of patients across disease stages (to a lesser extent) and response to treatment (SVR) for patients with cirrhosis. For genotype 2 and 3 patients the ICER becomes positive (positive incremental cost and positive incremental QALYs) for the scenarios where age at entry is increased by 10 years and where all treated patients have mild chronic HCV. These are the only scenarios (other than a change in discounting practice where costs are discounted at 6% and outcomes at 1.5%), where treatment for genotype 2 and 3 patients with HCV/HIV co-infection is not dominant.

Increasing the age at which patients enter the model by 15 years leads to an approximate doubling of the ICER for genotype 1 and 4 patients – the QALY gain with treatment is reduced by around one-third. Similarly, alternative assumptions regarding the stage of liver disease in which patients enter the model has a large impact on the ICER, with less favourable results associated with patients being in the earlier (lower fibrosis) stages of disease. Reducing response to treatment for patients with cirrhosis at baseline also leads to less favourable cost-effectiveness estimates.

Probabilistic sensitivity analysis

In a PSA, where the probabilities of achieving SVR, health-state costs, health-state utility values, and transition probabilities for the natural history parameters are sampled probabilistically, treatment of co-infected patients with genotypes 1 and 4 is associated with increased QALYs (with a range from 0.09 to 1.49 QALYs), but typically also increased costs (ranging from –£447 to £9022) when compared with BSC (*Table 71* and *Figure 18*). While treatment for patients with genotypes 2 and 3 is also associated with increased QALYs (from 0.09 to 3.63 QALYs gained), in approximately 70% of simulations the incremental cost was negative (*Figure 19*).

TABLE 71 Mean costs and outcomes (percentile-based 95% CIs) for HCV/HIV co-infected patients with peginterferon alfa-2a and ribavirin combination therapy, from PSA

Genotype	Treatment	Lifetime costs (£)	QALYs
Genotypes 1 + 4	BSC	22,049 (15,040 to 30,554)	12.68 (11.71 to 13.48)
	PEG α-2a	28,035 (22,764 to 34,429)	13.42 (12.63 to 14.11)
	Incremental	5986 (3332 to 7993)	0.74 (0.33 to 1.15)
Genotypes 2 + 3	BSC	22,031 (15,443 to 30,254)	12.69 (11.81 to 13.53)
	PEG α-2a	20,456 (17,298 to 24,327)	14.51 (13.62 to 15.41)
	Incremental	–1575 (–7275 to 2673)	1.82 (0.91 to 2.81)

PEG α, peginterferon alfa.

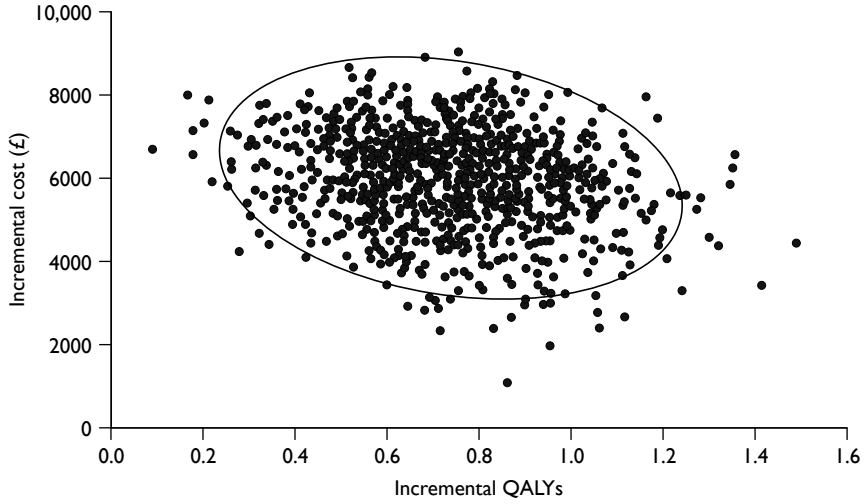

FIGURE 18 Cost-effectiveness plane for genotypes 1 and 4 – incremental cost and incremental QALYs for treatment of HCV/HIV co-infected patients with peginterferon alfa-2a and ribavirin combination therapy.

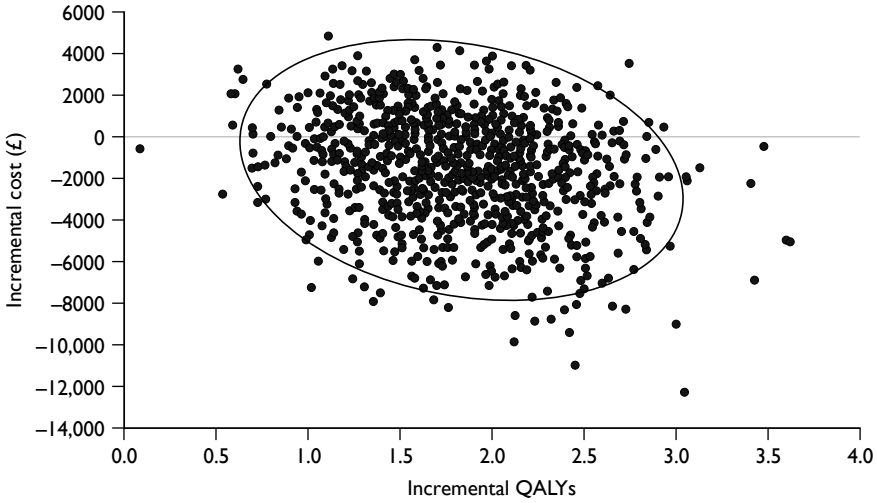

FIGURE 19 Cost-effectiveness plane for genotypes 2 and 3 – incremental cost and incremental QALYs for treatment of HCV/HIV co-infected patients with peginterferon alfa-2a and ribavirin combination therapy.

In this analysis, treatment using peginterferon alfa-2a and ribavirin combination therapy, for HCV/HIV co-infected patients with genotypes 1 and 4, had a probability of being cost-effective (compared with BSC) was 98% at a willingness-to-pay threshold of £20,000 per QALY, and 99% at a willingness-to-pay threshold of £30,000 per QALY (*Figure 20*). For patients with genotypes 2 and 3, treatment using peginterferon alfa-2a and ribavirin combination therapy had a probability of being cost-effective (compared with BSC) of 100% at a willingness-to-pay threshold of £20,000 per QALY.

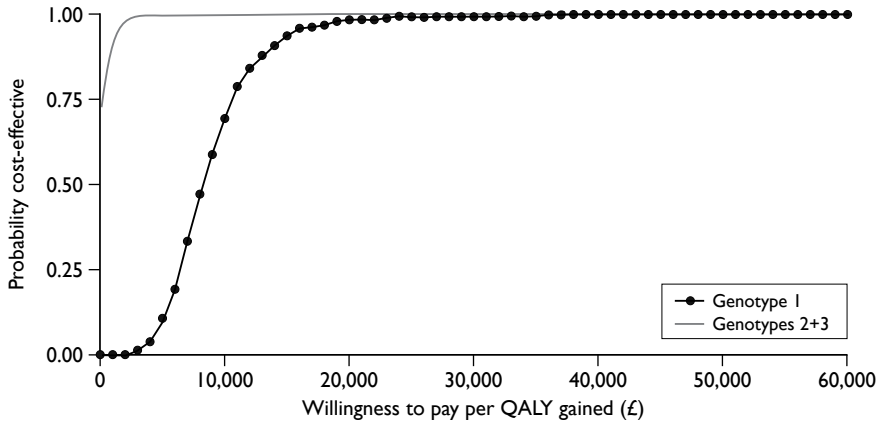

FIGURE 20 Cost-effectiveness acceptability curves for treatment of HCV/HIV co-infected patients with peginterferon alfa-2a and ribavirin combination therapy.

Peginterferon alfa-2b

Costs and outcomes modelled for patients co-infected with HCV/HIV receiving combination therapy with peginterferon alfa-2b and ribavirin are presented in *Table 72*.

The impact of treating this group of patients is to improve the predicted outcome (by 0.67 and 1.38 QALYs for genotypes 1 and 4 and genotypes 2 and 3, respectively) and to increase lifetime costs (by £7901 and £2989 QALYs for genotypes 1 and 4 and genotypes 2 and 3, respectively). The reduction in supportive care costs associated with disease progression in both groups of patients (genotypes 1 and 4 and genotypes 2 and 3) is insufficient fully to offset the additional costs of antiviral treatment.

As described above, the cost-effectiveness results in *Table 72* do not take account of uncertainties regarding the potential impact of HIV co-infection on the natural history of HCV infection, overall mortality, utility gains from successful treatment or additional costs of on-treatment monitoring. *Table 73* reports the cost-effectiveness results from the model after applying the RRs for disease progression[25] to the baseline risks in the natural history model. This suggests that treatment using peginterferon alfa-2b and ribavirin combination therapy will be more cost-effective in HCV/HIV co-infected patients, if the risks of fibrosis progression are greater than for mono-infected patients, as the incremental cost associated with providing treatment is lower and incremental QALY gain is greater than in the base case. In this analysis peginterferon alfa-2b is dominant (produces improved outcomes at lower cost) compared with supportive care for patients with genotypes 2 and 3.

Table 74 reports the cost-effectiveness results from the model when the age-specific mortality risks are doubled, for HCV/HIV co-infected patients. This reduces lifetime costs and QALYs for both peginterferon-treated and BSC cohorts, and would suggest that treatment using peginterferon alfa-2b and ribavirin combination therapy will be less cost-effective in HCV/HIV co-infected patients, if mortality risk is greater than for mono-infected patients.

Tables 75 and *76* report cost-effectiveness results from alternative assumptions on the utility gain for HCV/HIV co-infected patients who achieve an SVR – in the first case the utility gain is assumed to be half that reported for HCV mono-infected patients and in the second case the utility gain is assumed to be zero. In both cases the QALY gain from treatment with peginterferon is reduced, indicating that treatment using peginterferon alfa-2b and ribavirin combination

TABLE 72 Base-case cost-effectiveness for treatment of HCV/HIV co-infected patients with peginterferon alfa-2b and ribavirin combination therapy

Genotype	Treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	PEG α-2b	30,102	19.38	13.32	
	Incremental	7901	0.46	0.67	11,806
Genotypes 2 + 3	BSC	22,201	18.93	12.65	
	PEG α-2b	25,190	19.83	14.03	
	Incremental	2989	0.91	1.38	2161

PEG α, peginterferon alfa.

TABLE 73 Cost-effectiveness of treatment of HCV/HIV co-infected patients with peginterferon alfa-2b and ribavirin combination therapy – using higher fibrosis progression probability for co-infected patients

Genotype	Treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotypes 1 + 4	BSC	31,839	16.91	10.90	
	PEG α-2b	37,465	17.84	11.98	
	Incremental	5626	0.93	1.08	5193
Genotypes 2 + 3	BSC	31,839	16.91	10.90	
	PEG α-2b	30,327	18.76	13.10	
	Incremental	–1513	1.85	2.20	PEG α-2b dominates

PEG α, peginterferon alfa.

TABLE 74 Cost-effectiveness of treatment of HCV/HIV co-infected patients with peginterferon alfa-2b and ribavirin combination therapy – using higher age-specific mortality risks for co-infected patients

Genotype	Treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotypes 1 + 4	BSC	19,865	17.46	11.70	
	PEG α-2b	28,309	17.80	12.25	
	Incremental	8445	0.35	0.55	15,472
Genotypes 2 + 3	BSC	19,865	17.46	11.70	
	PEG α-2b	23,929	18.14	12.84	
	Incremental	4065	0.68	1.14	3570

PEG α, peginterferon alfa.

therapy will be less cost-effective in HCV/HIV co-infected patients, if utility gain from SVR is lower in HCV/HIV co-infected patients than for mono-infected patients.

A final scenario analysis was performed to consider the impact of on-treatment monitoring costs on the cost-effectiveness of antiviral treatment for HCV/HIV co-infected patients. *Table 77* reports the cost-effectiveness results from the model if on-treatment costs for HCV/HIV co-infected patients are assumed to be double those for HCV mono-infected patients. As with the previous analyses this assumption suggests that treatment using peginterferon alfa-2b and ribavirin combination therapy is less cost-effective than in the base case.

TABLE 75 Cost-effectiveness of treatment of HCV/HIV co-infected patients with peginterferon alfa-2b and ribavirin combination therapy – reducing the utility gain for SVR by half

Genotype	Treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	PEG α-2b	30,102	19.38	13.19	
	Incremental	7901	0.46	0.54	14,733
Genotypes 2 + 3	BSC	22,201	18.93	12.65	
	PEG α-2b	25,190	19.83	13.77	
	Incremental	2989	0.91	1.12	2669

PEG α, peginterferon alfa.

TABLE 76 Cost-effectiveness of treatment of HCV/HIV co-infected patients with peginterferon alfa-2b and ribavirin combination therapy – no utility gain for patients achieving SVR

Genotype	Treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	PEG α-2b	30,102	19.38	13.05	
	Incremental	7901	0.46	0.40	19,590
Genotypes 2 + 3	BSC	22,201	18.93	12.65	
	PEG α-2b	25,190	19.83	13.51	
	Incremental	2989	0.91	0.86	3489

PEG α, peginterferon alfa.

TABLE 77 Cost-effectiveness of treatment of HCV/HIV co-infected patients with peginterferon alfa-2b and ribavirin combination therapy – using higher on-treatment monitoring costs for co-infected patients

Genotype	Treatment	Cost (£)	Outcome (life-years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	PEG α-2b	31,153	19.38	13.32	
	Incremental	8952	0.46	0.67	13,376
Genotypes 2 + 3	BSC	22,201	18.93	12.65	
	PEG α-2b	26,241	19.83	14.03	
	Incremental	4040	0.91	1.38	2921

PEG α, peginterferon alfa.

Deterministic sensitivity analysis

Table 78 reports the results of a DSA for treatment of HCV/HIV co-infected patients using peginterferon alfa-2b and ribavirin combination therapy. These suggest that the results are robust to a change in structural assumptions (allowing spontaneous SVR from the mild chronic HCV state), the proportion of the baseline cohort that is male and cost of the SVR health state. Reducing drug acquisition costs has the effect of reducing the ICER, as might be expected as it reduces the drug costs while the outcome difference is unchanged.

The greatest variability in ICERs is associated with changes in the age at which patients enter the model, the distribution of patients across disease stages (to a lesser extent) and response to treatment (SVR) for patients with cirrhosis. Increasing the age at which patients enter the model

TABLE 78 Deterministic sensitivity analysis for treatment of HCV/HIV co-infected patients with peginterferon alfa-2b and ribavirin combination therapy

	Genotype 1			Genotypes 2 + 3		
	Incremental cost (£)	Incremental QALY	ICER	Incremental cost (£)	Incremental QALY	ICER
Base case	7901	0.67	11,806	2989	1.38	2161
Structural uncertainty						
Spontaneous SVR from mild (0.002)	8093	0.63	12,893	3369	1.30	2590
Spontaneous SVR from mild (0.010)	8005	0.65	12,376	3194	1.34	2386
Discount cost and outcome at 0%	2727	1.70	1607	–7250	3.42	–2122
Discount cost at 6%, outcome at 1.5%	9539	1.11	8586	6231	2.26	2760
Baseline cohort characteristics						
Cohort 80% male	7927	0.66	11,957	3,041	1.37	2219
Cohort 40% male	7819	0.69	11,350	2,827	1.42	1988
Change average age of cohort at start of simulation (base case 40 years old)						
–10 years	7329	0.83	8819	1857	1.70	1090
+5 years	8268	0.58	14,192	3715	1.21	3066
+10 years	8688	0.49	17,573	4547	1.04	4384
+15 years	9157	0.41	22,499	5475	0.86	6336
Change distribution of cohort across disease stages at start of simulation						
Cohort 100% mild chronic HCV	10,442	0.47	22,104	8018	0.99	8070
Cohort 100% moderate HCV	6213	0.78	7934	–351	1.61	–218
Cohort 100% CC	3640	1.07	3390	–5443	2.18	–2493
Parameter uncertainty						
Assume SVR is 25% lower in patients with CC	8133	0.64	12,690	3448	1.33	2599
Assume SVR is 50% lower in patients with CC	8365	0.61	13,656	3907	1.27	3075
Cohort 100% CC, assume SVR is 25% lower in patients with CC	5960	0.79	7541	–852	1.62	–525
Cohort 100% CC, assume SVR is 50% lower in patients with CC	8280	0.51	16,334	3738	1.06	3521
Transition probability from mild-to-moderate disease = 0.04	7584	0.72	10,483	2361	1.49	1585
Transition probability from moderate disease to CC = 0.073	7226	0.82	8762	1654	1.69	978
Cost of SVR state = £0	7830	0.67	11,700	2849	1.38	2060
Reduce cost of PEG α-2b by 20%	6340	0.67	9473	1428	1.38	1033
Reduce cost of PEG α-2b by 30%	5560	0.67	8307	648	1.38	468
Reduce cost of RBV by 20%	7246	0.67	10,827	2334	1.38	1688
Reduce cost of RBV by 30%	6918	0.67	10,337	2006	1.38	1451

CC, compensated cirrhosis; PEG α, peginterferon alfa; RBV, ribavirin.

by 15 years leads to an approximate doubling of the ICER for genotype 1 and 4 patients – the QALY gain with treatment is reduced by around one-half for both genotype 1 and 4 patients and genotype 2 and 3 patients. Alternative assumptions regarding the stage of liver disease in which patients enter the model has a large impact on the ICER, with less favourable results associated with patients being in the earlier (lower fibrosis) stages of disease. Reducing response

to treatment for patients with cirrhosis at baseline also leads to less favourable cost-effectiveness estimates, while increasing the probability of fibrosis progression for early disease states leads to more favourable cost-effectiveness results.

Probabilistic sensitivity analysis

In a PSA, where the probabilities of achieving SVR, health-state costs, health-state utility values and transition probabilities for the natural history parameters were sampled probabilistically, treatment of co-infected patients with genotypes 1 and 4 is associated with increased QALYs (with a range from 0.1 to 1.41 QALYs), but also increased costs (ranging from £4260 to £10,560) in all simulations when compared with BSC (*Table 79* and *Figure 21*). Treatment for patients with genotypes 2 and 3 is also associated with increased QALYs (from 0.22 to 2.72 QALYs gained) and generally with increased costs. In approximately 7% of simulations the incremental cost was negative (*Figure 22*).

In this analysis, treatment using peginterferon alfa-2b and ribavirin combination therapy for patients with genotypes 2 and 3 had a probability of being cost-effective (compared with BSC) of 100% at a willingness-to-pay threshold of £20,000 per QALY – see *Figure 23*. For patients with genotypes 1 and 4 the probability of being cost-effective (compared with BSC) was 90% at a willingness-to-pay threshold of £20,000 per QALY and 99% at a willingness-to-pay threshold of £30,000 per QALY.

TABLE 79 Mean costs and outcomes (percentile-based 95% CIs) for HCV/HIV co-infected patients using peginterferon alfa-2b and ribavirin combination therapy, from PSA

Genotype	Treatment	Lifetime costs (£)	QALYs
Genotypes 1 + 4	BSC	22,175 (15,557 to 30,351)	12.70 (11.89 to 13.51)
	PEG α-2b	30,086 (24,839 to 36,244)	13.37 (12.66 to 14.07)
	Incremental	7910 (5593 to 9673)	0.66 (0.32 to 1.06)
Genotypes 2 + 3	BSC	22,010 (15,706 to 30,199)	12.70 (11.85 to 13.56)
	PEG α-2b	25,105 (21,202 to 30,212)	14.06 (13.26 to 14.85)
	Incremental	3095 (–1241 to 6340)	1.36 (0.69 to 2.01)

PEG α, peginterferon alfa.

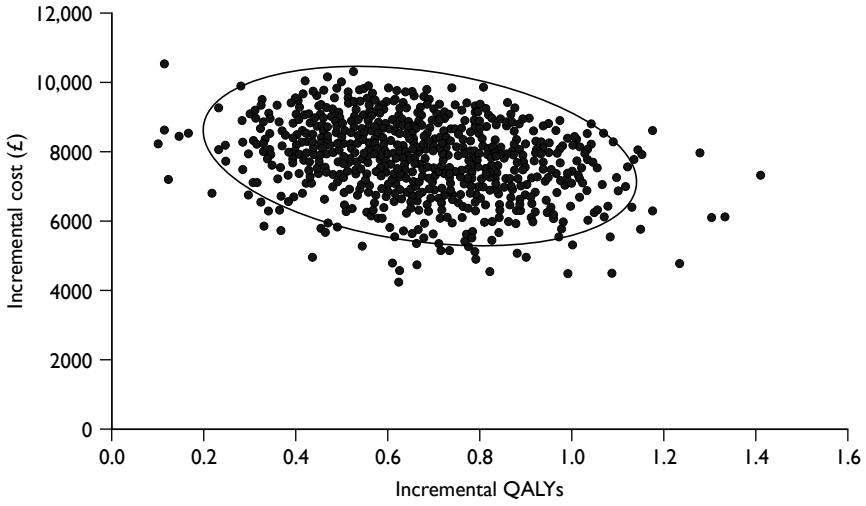

FIGURE 21 Cost-effectiveness plane for genotypes 1 and 4 – incremental cost and incremental QALYs for treatment of HCV/HIV co-infected patients with peginterferon alfa-2b and ribavirin combination therapy.

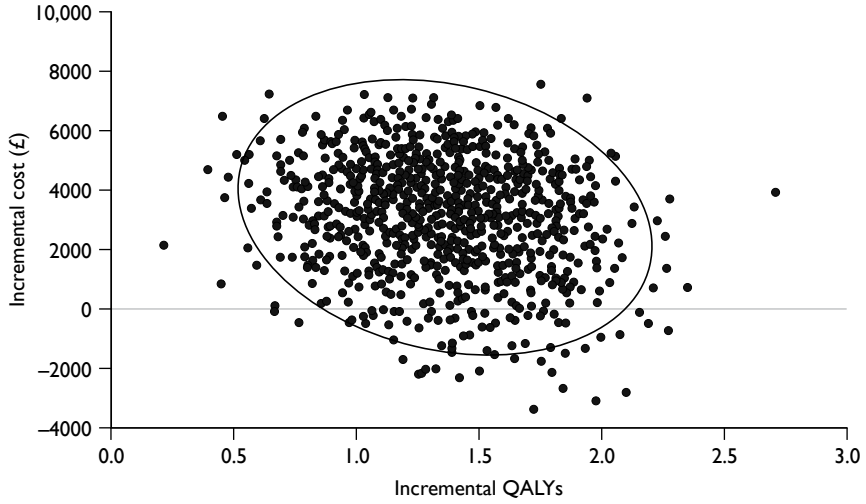

FIGURE 22 Cost-effectiveness plane for genotypes 2 and 3 – incremental cost and incremental QALYs for treatment of HCV/HIV co-infected patients with peginterferon alfa-2b and ribavirin combination therapy.

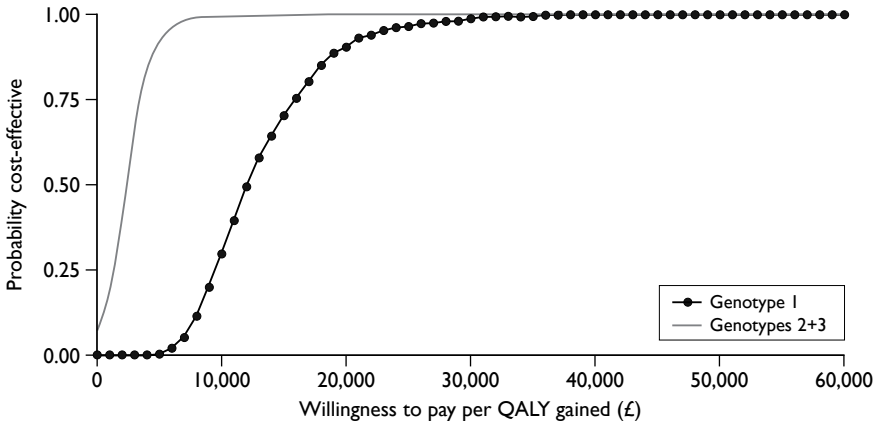

FIGURE 23 Cost-effectiveness acceptability curves for treatment of HCV/HIV co-infected patients with peginterferon alfa-2b and ribavirin combination therapy.

Summary of key results

Systematic review of published cost-effectiveness and QoL evidence

- A systematic search of the literature found two fully published economic evaluations that were relevant to the scope of this assessment. Both economic evaluations used Markov models to extrapolate from SVRs, reported in clinical trials, to life expectancy and (in one case) quality-adjusted life expectancy gains associated with antiviral treatment strategies for patients who were co-infected with HCV and HIV. One of the evaluations[64] based its analysis on data from trials that included only patients mono-infected with HCV, while the other[65] used data from trials including co-infected patients. Both evaluations indicated that HCV antiviral treatment was associated with gains in life expectancy for HCV/HIV co-infected patients. Both evaluations were conducted in the context of the US health-care system.
- A systematic search for published studies of HRQoL found no relevant studies.

Roche submission to NICE

- Roche submitted a dossier[104] in support of peginterferon alfa-2a combined with ribavirin in three subgroups of patients:
  - shortened duration of treatment for patients with LVL who exhibit an RVR
  - re-treatment in patients who did not respond or relapsed on previous treatment with peginterferon
  - treatment of patients with HCV/HIV co-infection.
- The submission included model-based economic evaluations using clinical effectiveness data from published RCTs, although effectiveness evidence for shortened treatment duration was derived from subgroup analyses. A number of the clinical effectiveness studies included by the manufacturer do not make the comparisons specified by NICE (patients who did not respond[88] or relapsed,[89] and patients with HCV/HIV co-infection[66]). Most commonly, these trials had an active comparator, rather than supportive care. In the majority of situations the comparison with supportive care assumed that the spontaneous SVR rate will be zero, which generally accords with clinical opinion.
- Roche's model is structurally similar to that used in our previous assessment report[17] for NICE TA106. The natural history parameters in the model are also similar to our previous assessment report,[17] as are the health-state utilities – except for the SVR state which in the manufacturer's model are age-specific values derived in a general population. The differences in structural assumptions and utility values appear likely to produce higher estimates of utility gain associated with SVR.
- The economic evaluation section of the MS does not indicate clearly where the clinical effectiveness parameters (EVR and SVR) are presented and critically appraised in the clinical effectiveness section of the MS. As a result there is no discussion or critical analysis of the reliability or generalisability of the clinical effectiveness evidence used to populate the model.
- Shortening the duration of treatment results in a QALY loss compared with standard treatment duration, as a result of a slight reduction in SVR, as well as a reduction in costs. As both costs and outcomes are lower with shortened treatment duration, the ICERs are positive (in the south-west quadrant of the cost-effectiveness plane) – £15,472 for genotype 1 and 4 patients and £2719 for genotype 2 and 3 patients. The MS does not discuss the appropriate approach or decision rules to interpret ICERs for cost-saving and QALY-reducing interventions.
- Two separate populations of re-treated patients were modelled: patients who relapsed following treatment with peginterferon and patients who did not respond to initial treatment with peginterferon. For relapsing patients the model estimates a QALY gain and a reduction in total costs, compared with BSC, suggesting that re-treatment with peginterferon is dominant. This is based on data from an RCT that may not be generalisable to all relapsed patients. Re-treatment of non-responding patients results in QALY gains compared with BSC, but also increased costs – the estimated reduction in costs of managing progressive liver disease in the cohort of patients receiving antiviral treatment does not fully offset treatment costs – resulting in positive ICERs (in the north-east quadrant of the cost-effectiveness plane).
- For patients with HCV/HIV co-infection the MS reports a comparison with non-peginterferon, using effectiveness data from APRICOT,[66] suggesting that peginterferon dominates non-peginterferon. This does not meet the scope issued by NICE, which specifies that peginterferon be compared with BSC. We extended the analysis conducted by the manufacturer (applying the same assumption as that adopted for non-responding or relapsing patients – that the SVR rate for untreated patients would be zero), estimating a QALY gain (using the manufacturer's model) of 1.95 and incremental cost of £1765, resulting in an ICER of £903 per QALY gained.
- Deterministic sensitivity analyses reported in the MS suggested that the results are generally robust to variation in a limited number of parameters that were not included in the PSAs.

These included longer duration of surveillance following SVR, average patient weight, start age and proportion of women in the modelled cohort.

- We undertook further analyses of the manufacturer's model examining the robustness of the results in the MS to changes in assumptions regarding the:
  - utility value for patients achieving an SVR
  - distribution of patients across stages of progressive liver disease
  - inclusion of chronic disease management costs alongside treatment costs.
- These additional analyses generally resulted in less favourable ICERs but did not substantially alter the conclusions from the MS.

Schering-Plough submission to NICE

- Schering-Plough submitted a dossier[92] in support of peginterferon alfa-2b combined with ribavirin in two of the three subgroups of patients within the scope of the NICE appraisal:
  - re-treatment in patients who did not respond or relapsed on previous treatment with peginterferon
  - treatment of patients with HCV/HIV co-infection.
- The submission included model-based economic evaluations based on clinical data from a multicentre, non-randomised, open-label uncontrolled study (for re-treatment in non-responding or relapsing patients) and a Phase III open-label trial[95] (for patients with HCV/HIV co-infection). As the included studies do not make the comparisons specified by NICE (antiviral treatment compared with BSC), the manufacturer has assumed that the spontaneous SVR rate for moderate chronic HCV and compensated cirrhosis (applied to BSC patients) will be zero; this would generally accord with clinical opinion. The model includes a low spontaneous SVR probability for patients with mild chronic HCV; this is applied to patients in the BSC and active treatment cohorts.
- The manufacturer's model is structurally similar to that used in our previous assessment report for NICE.[17] However, it does not distinguish between patients achieving an SVR from any of the treatment-eligible states (mild or moderate HCV and compensated cirrhosis). Utility estimates published from the UK Mild Hepatitis C Trial[82] would suggest that these states should be separate. The natural history parameters in the model are similar to those adopted for our previous assessment report for NICE,[17] as are the health-state utilities and health-state costs (inflated from 2003–4 to 2007–8 costs using the HCHS Pay and Prices Index[85]).
- No systematic searches for health-state utilities or costs are reported. The manufacturers did not report a critical appraisal of the EPIC3,[96] Scotto and colleagues[97] or Laguno and colleagues[95] trials, which provided the clinical effectiveness data for the model and sensitivity analyses. It is therefore difficult to judge the reliability or generalisability of the data used to populate the model. Costs and health-state utilities were primarily derived from the Mild Hepatitis C Trial.[82]
- Two groups of patients were modelled in the Schering-Plough submission;[92] the first of these was re-treated and relapsed patients, each based upon data from the EPIC3[96] clinical study report. In the group of 'non-responders' overall in the Schering-Plough submission,[92] peginterferon and ribavirin combination therapy cost £26,666, with a QALY gain of 1.04 over no treatment, resulting in an ICER of £4387 per QALY gained. For genotypes 1 and 4, these results were £27,125, with a 0.7 QALY gain and an ICER of £7177 per QALY gained. For genotypes 2 and 3, costs of £24,301 and a QALY gain of 2.78 resulted in an ICER of £783 per QALY gained.
- The second group included in this submission was patients co-infected with HCV/HIV, and modelled using effectiveness data from the Laguno and colleagues trial.[95] In this group overall, peginterferon and ribavirin combination therapy cost £26,997, with a QALY gain of 2.32, which resulted in an ICER of £1077. For genotypes 1 and 4 in this group, peginterferon-plus-ribavirin combination therapy cost £27,790, with a QALY gain of 2.01, giving an ICER

of £1637; in genotypes 2 and 3, a cost of £25,645 and QALY gain of 2.85 resulted in an ICER of £403 per QALY gained.

- The DSA showed that the ICERs in both the re-treated and co-infected cohorts were sensitive to variation in the EVR and SVR, and to changes in patient weight. In the re-treatment group, ICERs showed a small increase in response to changes in disease severity distribution within the patient group. The ICERs in this group appeared very sensitive to (and increased substantially with) the substitution of data from the Scotto and colleagues study[97] with the EPIC3 trial.[96] Where discounting was removed, the ICER reduced to £1265 per QALY gained in the re-treatment group. In the HCV/HIV co-infection group, peginterferon and ribavirin combination therapy was dominant where discounting was removed.
- Probabilistic sensitivity analyses were conducted including the majority of parameters in the model. Appropriate distributions appear to have been used. Three PSAs are presented for each patient group (re-treated and HCV/HIV co-infected), including the overall cohort, and then separate analyses for genotype subgroups. The PSA reports high probabilities (over 90%) of treatment with peginterferon alfa-2b being cost-effective at a willingness-to-pay threshold of £20,000 and £30,000.

SHTAC independent economic analysis

- We adapted a previously published model to undertake an independent economic assessment of shortened treatment duration with peginterferon alfa, using clinical effectiveness data included in this review. Our economic model was structurally similar to those developed by the manufacturers, using similar input parameters to model disease progression, health-state costs and utility. The model consists of nine non-absorbing health states representing stages of chronic liver disease and one absorbing state representing death.
- The economic model contains three health states (SVR) representing cure of chronic HCV, which are differentiated by the patient's stage of disease (mild HCV, moderate HCV and compensated cirrhosis) prior to treatment, as these are expected to have an impact on subsequent risk of progressive liver disease, post-treatment surveillance and also HRQoL. The remaining six, non-absorbing states (mild HCV, moderate HCV, compensated and decompensated cirrhosis, HCC and liver transplant) represent stages of progressive liver disease. Patients not exhibiting an SVR are expected to face the same risk of disease progression as untreated patients. These assumptions are all consistent with our previous assessments, and other published economic evaluations of antiviral treatment for chronic HCV. The model has a cycle length of 1 year and incorporates a half-cycle adjustment.
- Baseline populations in the model were based on a clinical audit undertaken at a London teaching hospital. These differentiated between new and existing patients in terms of average age and the distribution of patients across stages of chronic liver disease (mild HCV, moderate HCV and compensated cirrhosis). The proportion of men in the baseline cohort was based on our previous assessment. The majority of these assumptions do not affect response to treatment, but relate to patients' risk of all-cause mortality. The influence of stage of chronic liver disease on response to treatment (and the effect on cost-effectiveness of intervention) was assessed in a sensitivity analysis.
- Sustained virological responses extracted from clinical trials included in the clinical effectiveness review are used in the model to estimate the probability of treatment-eligible patients transitioning to a relevant SVR state. Where applicable, EVRs are used to estimate the average duration of treatment and total drug acquisition costs for each antiviral treatment strategy. Early stopping of treatment in patients unlikely to achieve an SVR can have a significant impact on the cost-effectiveness of treatment with peginterferon alfa.
- Our clinical effectiveness systematic review included five trials of shortened treatment duration used in our economic evaluation (three for genotype 1 patients, one for genotype 2 only and one for genotypes 2 and 3 combined):

  - Shorter duration of treatment (from 48 to 24 weeks) with peginterferon alfa-2a for the subgroup of genotype 1 patients with baseline LVL and who achieve an RVR reduced total costs by approximately one-third, but was also associated with slightly poorer outcome. The ICERs were positive (as both incremental cost and incremental QALYs are negative) and ranged from around £34,000 per incremental QALY to £65,000 per incremental QALY. As these ICERs are derived as the ratio of two negative numbers, the commonly assumed decision rule – Is the ICER below a given (arbitrary) threshold? – does not hold. In this situation the logic is reversed and ICERs below the threshold are rejected. This can be better interpreted using the net benefits framework.
  - Shorter duration of treatment (from 24 to 16 weeks) with peginterferon alfa-2a for genotype 2 and 3 patients reduced total costs by approximately one-quarter, and was associated with better outcome in the included trials. In these scenarios, there was shortened treatment duration for the subgroup of genotype 2 or 3 patients with low baseline viral load and who achieved an RVR-dominated standard duration.
  - Shorter duration of treatment (from 48 to 24 weeks) with peginterferon alfa-2b for the subgroup of genotype 1 patients with baseline LVL and who achieve an RVR was associated with a reduction in costs of approximately £9000. Combined with a QALY gain increase of 0.49, this resulted in peginterferon alfa-2b dominating the standard 48-week duration of treatment.
- None of the RCTs identified by our searches, which examined re-treatment of patients previously treated with peginterferon or that assessed peginterferon treatment in patients with HCV/HIV co-infection, met the inclusion criteria. The analyses of these patient subgroups have used data that have not been formally quality assessed in the same way as for the review of shortened treatment duration.
- Re-treatment, with peginterferon alfa-2a, of patients who did not respond to previous peginterferon therapy increased costs (by approximately 62% in patients with genotype 1, and approximately 25% in genotype non-1 patients). The QALY gain from treatment was 0.31 for genotype 1 patients and 0.59 for genotype non-1 patients. This resulted in positive ICERs for both groups: in genotype 1 patients this was £52,587 per QALY gained and in genotype non-1 patients this was £10,926 per QALY gained.
- Where an 'early stopping rule' at 12 weeks for patients not demonstrating an EVR was applied to re-treated patients the incremental cost increase was substantially reduced by approximately 12% (£3398) in genotype 1 patients, and by approximately 5% (£1415) in genotype non-1 patients. The QALY gain increased slightly in both groups (to 0.37 in genotype 1 and 0.62 in genotype non-1). Accordingly the ICERs for each group, while remaining positive, reduced to £9169 per QALY gained in genotype 1 and £2294 per QALY gained in genotype non-1.
- Sustained virological responses for the re-treated patients receiving peginterferon alfa-2b were taken from the Schering-Plough MS. The impact of re-treating patients with genotypes 1 and 4, was an increase in costs of £9380, and in QALYs of 0.39, resulting in an ICER of £23,912. For genotypes 2 and 3 these costs were reduced by £989 and QALYs increased by 1.72, resulting in peginterferon alfa-2b dominating BSC.
- Where an early stopping rule is applied for patients not demonstrating an EVR in genotypes 1 and 4, the incremental costs reduce to £3256 and the QALY gain increases to 0.42, resulting in an ICER of £7681. In genotypes 2 and 3 the incremental costs are reduced further, to –£2850, and the QALY gain increased slightly.
- For patients that are co-infected with HCV/HIV, treatment with peginterferon alfa-2a resulted in a QALY gain of 0.75 for genotypes 1 and 4, and 1.86 for genotypes 2 and 3. Costs also increased by approximately 27% (£5932) in genotypes 1 and 4, which resulted in a positive ICER of £7941 per QALY gained in this group. Costs decreased overall as a result of treating genotypes 2 and 3 by approximately 8%, a reduction of £1717. This resulted in peginterferon alfa-2a dominating BSC in this group of patients.

- For patients that are co-infected with HCV/HIV, treatment with peginterferon alfa-2b resulted in increased costs for both genotypes 1 and 4 and genotypes 2 and 3 (of £7901 and £2989, respectively); the QALY gain also increased by 0.67 and 1.38, respectively. ICERs for both groups were positive: in genotypes 1 and 4 this was £11,806 per QALY gained, and in genotypes 2 and 3 this was £2161 per QALY gained.

Strengths, limitations and generalisability

- The majority of the clinical trials used to model response to treatment (SVR and, where relevant, EVR) were not included in our systematic review, and have not been fully critically appraised. Only clinical trials relating to shortened treatment duration were included. In the case of re-treated patients and those with HCV/HIV co-infection, no trials were found that met the scope for this appraisal (of having placebo or supportive care control arms). As a result, the model uses clinical trial data that have not been assessed for risk of bias. The effectiveness data for patients with HCV/HIV co-infection have been extracted from published systematic reviews/meta-analyses (see *Appendix 9*) and, although these were quality assessed during the process of the published reviews, they have not been quality assessed or critically assessed in our current review.
- Some of the effectiveness data included in the model have been taken from comparatively small trials (20–40 patients per arm) that were not adequately powered to detect differences in SVR, or were derived from subgroups of patients in larger trials. In some cases the reporting of outcomes has not been consistent – for example, von Wagner and colleagues[56] report SVR for patients with RVR and LVL, whereas Yu and colleagues[55] report SVR for patients with RVR but do not stratify this result by viral load.
- The proportion of patients with different genotypes in multinational clinical trials is unlikely to be reflective of the genotype distribution in the UK. Hence, the overall SVR is unlikely to provide a good indication of response. As a result, where possible, patient genotypes have been modelled separately adopting commonly used groupings of 'difficult-to-treat' genotypes (genotype 1 and, occasionally, genotype 4) and more responsive genotypes (2 and 3).
- Baseline populations applied in the economic model were based on data for new and existing patients from a clinical audit in a liver unit at a London teaching hospital.[102] Clinical advisors to this project confirmed that the distribution of patients across disease stages agreed with their clinical experience. However, it is not clear how closely these distributions, or the assumed mean age of patients at the start of the model, relate to the characteristics of patients in the subgroups of patients covered by this review. The clinical audit data pre-date NICE guidance on the use of peginterferons in patients with chronic HCV (TA75[38] and TA106[33]) and it is not clear how the distribution of patients across disease stages may have changed, particularly given recent guidance on treating patients with mild disease (TA106[33]). However, there is generally very little information on the age and stage of disease for treated patients – the latter becoming less relevant to decisions to initiate treatment but remaining relevant to modelling response to treatment where patients with cirrhosis appear less likely to achieve SVR.
- Disease progression parameters included in the model were derived from large cohort studies in relevant (European) populations. The parameters have been used in previous economic evaluations[17,81] and ensure consistency between appraisals. Input parameters for fibrosis progression (from mild-to-moderate and from moderate-to-compensated cirrhosis) were taken from a recent analysis using biopsy data from a UK cohort study.[18,82] Where evidence suggests that differential progression rates should be applied for the subgroups covered by this assessment (e.g. fibrosis progression in HCV/HIV co-infected patients), this has been addressed in additional analyses in this report.
- Quality of life/health-state utility weights in the model were taken from reports on a multicentre trial and observational study,[81,82] conducted using the EQ-5D and valued using the UK general population tariff.[84] The population of patients recruited to the UK trial were

treatment-naive patients with mild HCV, and this was supplemented by an observational study recruiting patients with compensated and decompensated cirrhosis. It is not clear how applicable these QoL weights are to some of the subgroups of patients in the current assessment – re-treated patients are likely to be older, whereas QoL assessments for mono-infected patients may not be directly applicable to those with HCV/HIV co-infection.

- Health-state costs included in the model, taken from the UK Mild Hepatitis C Trial,[81,82] were developed in an observational study alongside the trial. Intervention costs were based on treatment protocols developed as part of our previous assessment[17] in collaboration with UK clinical experts and valued using reference costs from an NHS hospital trust. All costs were inflated to current costs using the HCHS Pay and Prices Index.[85] It is not clear how adequately the treatment protocols may capture the complexity of managing patients with HCV/HIV co-infection – the sensitivity of the cost-effectiveness results to the costs of managing antiviral treatment in this group of patients was addressed in a sensitivity analysis.

Chapter 6

Assessment of factors relevant to the NHS and other parties

It should be acknowledged that the lower limits of detection for HCV RNA in terms of RVR and SVR differed slightly between the RCTs included in our systematic review of clinical effectiveness, according to the different assays used. For example, RVR was defined as HCV RNA < 50 IU/ml in three of the trials, < 25 IU/ml in one trial, < 600 IU/ml in one trial and < 615 IU/ml in another. Although a detectable HCV viral load of 50 IU/ml or above is generally considered indicative of infection, thresholds of detectability are becoming lower as more sophisticated assays are being produced. It is therefore important to achieve standardisation in definitions of virological response, particularly given the increased emphasis on using RVR to determine optimum treatment duration. Similarly, there is a lack of clarity regarding thresholds for LVL and high viral load. The SPC for the two peginterferons vary in terms of what they consider to be LVL (varying between < 600,000 IU/ml and ≤ 800,000 IU/ml). Again, clarity is needed regarding viral load thresholds to ensure consistent clinical management of patients.

If patients with specific genotypes meeting the licence criteria received shortened courses of antiviral treatment, then they would benefit in terms of reduced exposure to adverse effects, which can be very unpleasant and have a profound impact on a person's day-to-day life, as well as that of family and carers. Consequently, it may also mean that less time is lost from work, thereby having an impact on economic circumstances.

Initiatives to encourage people who may have put themselves at risk of HCV infection, such as the Department of Health's 'FaCe It' campaign, need to be maintained to reduce the substantial pool of undiagnosed infection. As well as the government, the voluntary sector also plays a key role in public awareness raising. Efforts to identify HCV infections need to be augmented by appropriate methods of referral to specialist care for further investigation and, if appropriate, antiviral treatment. Referral mechanisms need to be effective to ensure that as many eligible patients progress through the care pathway to be successfully treated. Strategies are also needed to motivate patients to attend assessment appointments and to complete the full course of therapy. This may be more problematic for patients with co-infection with HIV, 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, as well as general practitioners and other services. However, these may be time and resource intensive, and will be subject to budget constraints.

In terms of implementation issues, there do not appear to be any significant barriers to diffusion of the appraised treatments into routine practice. Peginterferon alfa has been the standard of care for some time. Specialist hepatology nurses will already be familiar with the administration of these drugs in the treatment of HCV. However, management protocols will need to be updated, where necessary, to ensure efficient testing for RVR and viral load to identify which patients are likely to be successfully treated with shorter courses.

Chapter 7

Discussion

Statement of principal findings

Clinical effectiveness

The results of six RCTs were included in this systematic review, all in patients who were eligible for shortened treatment duration. Treatment in patients with genotype 1 was evaluated in four trials,[52–54,59] genotype 2 in one trial[55] and genotypes 2 and 3 in one trial.[56] All studies compared standard treatment duration (48 weeks for genotype 1, 24 weeks for genotypes 2 and 3) to a shorter duration (24 or 16 weeks, respectively). In five of the RCTs the patients had LVL at baseline (based on mean viral load), while in one RCT[52] less than one-quarter of patients had LVL (defined as HCV RNA < 400,000 IU/ml) at baseline. However, it was included in our systematic review because SVRs were presented for the subgroup of those with LVL who attained an RVR (i.e. the patient subgroup meeting the licensed criteria for receiving shortened courses of therapy, and thus within the scope of the NICE appraisal). Note, however, that this subgroup constituted only 10% of the total study population. In only one trial[56] did all randomised patients consist of those with LVL and who achieved an RVR. In addition, none of the studies was powered for this subgroup and results should therefore be interpreted with caution.

In terms of demographic characteristics, three of the studies[53–55] were carried out in Asian (Taiwanese) populations and may therefore not be generalisable to the likely eligible population in a UK setting. In addition, the mode of HCV infection was not reported in most of the studies, which may have implications for the relevance to the UK HCV population. The methodological reporting and study quality varied between the included trials but was generally good, although there was a risk of selection bias in two studies,[56,59] where the randomisation procedure was unclear.

All of the trials reported SVR as the primary outcome measure. The evidence showed that in the subgroup of patients who achieved an RVR and had LVL at baseline, there were no statistically significant differences in SVR rates between groups who received the standard duration of treatment and those who received shortened courses, for both genotype 1 and genotypes 2 and 3. The SVR rates in genotype 1 patients are much higher than would normally be expected for this genotype, probably due to the fact that it is a highly select group of patients with favourable factors that increase the chance of response (e.g. LVL and RVR, generally mild-to-moderate HCV-related liver damage, absence of significant comorbidities or co-infections, absence of drug or alcohol abuse).

The evidence does suggest that patients in this subgroup can receive shorter courses of combination therapy without compromising SVR rates. However, only two of the trials[52,59] were designed to establish non-inferiority (one of which became a superiority trial when a significant difference in overall SVR rates was observed),[59] so it cannot necessarily be assumed that shortened and standard duration treatment are comparable. It should also be remembered that SVRs according to baseline LVL and RVR are based on subgroups (of varying sizes) of the randomised patients and are likely to be underpowered. The results of the trials in these subgroups should therefore be regarded as speculative.

Other outcome measures included virological response during treatment, relapse rate, biochemical response, histological response and adverse effects of treatment. The proportion of patients achieving an RVR was not statistically significantly different between treatment groups who received the standard duration of treatment compared with those who received shortened courses, regardless of genotype. Rates of RVR in genotype 2/3 patients were generally higher than in genotype 1 patients. In the one trial[54] reporting relapse rates in the subgroup of patients with LVL and RVR, rates were low and not significantly different between those treated for 24 versus 48 weeks. Rates of adverse events were reported only for treatment groups as a whole (rather than subgroups based on LVL and RVR). There was a trend for a lower incidence of adverse events in patients treated for a shorter duration in three trials,[53,54,56] although, on the whole, there were no statistically significant differences between treatment arms (where reported).

As stated in *Chapter 4* (*Quantity and quality of research available*), no RCTs in patients co-infected with HCV/HIV comparing peginterferon alfa with BSC met our inclusion criteria. There were also no RCTs of the re-treatment of patients who had failed to respond to, or relapsed from, peginterferon alfa with a subsequent course of peginterferon alfa, comparing against BSC. However, it should be acknowledged that there is a wider evidence base in these patient groups, notably for co-infected people, in whom peginterferon alfa is compared with non-peginterferon alfa. For example, Kim and colleagues[51] and Zhao and colleagues[50] both included the same six RCTs in their systematic review of the effectiveness of peginterferon alfa in the treatment of HCV/HIV co-infection (see *Appendix 8*). All but one of the six RCTs in these two systematic reviews compared peginterferon alfa (2a or 2b) with non-peginterferon alfa. Furthermore, studies evaluating shortened treatment courses were eligible for inclusion in this review only if they reported SVR in patients with RVR and LVL. There are likely to be other studies evaluating shortened treatment courses but which were not restricted to patients with LVL. It should also be acknowledged that there were no RCTs of peginterferon alfa monotherapy that met the inclusion criteria for our systematic review, for any of the patient groups considered in this NICE appraisal, thus limiting what can be recommended for this patient group.

Cost-effectiveness

Systematic review of existing cost-effectiveness evidence

A systematic search of the literature for published economic evaluations that were relevant to the scope of this assessment identified two studies – both in HCV/HIV co-infected patients. Both studies included non-peginterferon (in combination with ribavirin or monotherapy) as well as peginterferon (in combination with ribavirin or monotherapy) and no treatment (supportive care), and used Markov models to extrapolate from SVRs, reported in clinical trials, to life expectancy and to QALYs (in one of the studies). Only one of the evaluations[65] based its analysis on data from clinical trials including HCV/HIV co-infected patients. Both evaluations were conducted in the context of the US health-care system and were considered to be of limited relevance to the current assessment.

Cost-effectiveness evidence submitted by manufacturers

Two manufacturers submitted evidence to NICE, with respect to this assessment.

Roche submitted a dossier[104] in support of peginterferon alfa-2a combined with ribavirin in three subgroups of patients:

- shortened duration of treatment for patients with LVL who exhibit an RVR
- re-treatment in patients who did not respond or relapsed on previous treatment with peginterferon; relapsing and non-responding patients were treated as separate subgroups, using data from different clinical trials
- treatment of patients with HCV/HIV co-infection.

Schering-Plough submitted a dossier[92] in support of peginterferon alfa-2b combined with ribavirin in two subgroups of patients:

- re-treatment in patients who did not respond or relapsed on previous treatment with peginterferon
- treatment of patients with HCV/HIV co-infection.

In some cases the studies used by the manufacturers to estimate response to treatment with peginterferon do not make the comparisons specified by NICE (patients who did not respond or relapsed and also patients with HCV/HIV co-infection, where the specified comparator is supportive care). In the majority of situations the manufacturer has conducted the comparison with supportive care by assuming that the spontaneous SVR rate will be zero – this would generally accord with clinical opinion.

The manufacturers' economic models were structurally similar, but not identical, to that adopted for the previous assessment report for NICE[17] and generally adopted similar natural history parameters, health-state utilities and health-state costs. The structural differences, and the differences in parameter inputs between the manufacturers' models and that adopted for our previous assessment,[17] were considered to be likely to overestimate the utility gain from treatment. The assessment group undertook additional analyses to quantify the impact of these differences on the QALY gains from treatment and on the resulting ICER.

Roche submission[104]

Shorter treatment duration resulted in substantial reductions in antiviral treatment costs (49% lower for genotype 1 and 4 patients and 31% lower for genotype 2 and 3 patients) and lower total costs (including costs of managing progressive liver disease associated with chronic HCV infection). However, there was also a reduction in total QALYs for shorter treatment duration compared with standard treatment duration, as a result of a reduction in SVR. As both costs and outcomes are lower with shortened treatment duration, the ICERs are positive (in the south-west quadrant of the cost-effectiveness plane) – £15,472 for genotype 1 and 4 patients and £2719 for genotype 2 and 3 patients. The submission did not discuss the complications of interpreting ICERs for cost- and outcome-reducing strategies.

Re-treating patients who relapsed following previous peginterferon treatment was reported as dominating supportive care – yielding a gain of 2.7 QALYs while reducing total costs by approximately £6000. This arises from a high SVR observed in one trial, which may not be generalisable to other populations of relapsed patients. The majority of patients in the study were genotype 1 patients who had received a shorter duration of treatment than the current standard of care (24 rather than 48 weeks). The SVRs applied in the model for re-treatment of patients who did not respond to previous peginterferon treatment were lower than for relapsed patients. While treatment resulted in QALY gains compared with BSC, the estimated reduction in costs of managing progressive liver disease did not fully offset treatment costs, resulting in positive ICERs (in the north-east quadrant of the cost-effectiveness plane) – £3334 for genotype 1 patients and £809 for genotype non-1 patients. The majority of patients recruited to the trial of non-responders to previous peginterferon treatment were genotype 1. There were only 29 genotype non-1 patients (9% of the arm used to estimate effectiveness of treatment in the model), the majority (66%) of whom were genotype 4.

For patients with HCV/HIV co-infection, treatment with peginterferon was estimated to dominate non-peginterferon, using direct effectiveness evidence from the APRICOT study.[66] However, this is not the comparison specified in the scope issued by NICE. The assessment group extended the analysis – assuming that the SVR rate for untreated patients would be

zero – estimating a QALY gain (using the manufacturer's model) of 1.95 and incremental cost of £1765, for peginterferon compared with BSC, resulting in an ICER of £903 per QALY gained.

The cost-effectiveness results were generally robust to variation in a limited number of parameters included in a DSA reported in the MS. PSAs were conducted, including the majority of parameters in the model. While appropriate distributions appear to have been used for the PSA, the parameterisation of the distributions for some inputs does not appear to make best use of data reported in the submission. Moreover, there seems to have been a lack of consideration regarding logical relationships and potential correlation between model inputs. Rather than report the probability of cost-effectiveness at certain willingness-to-pay thresholds, the submission identified a maximum threshold of £15,000 for all analyses. Further analyses of the manufacturer's model undertaken by the assessment group generally resulted in less favourable ICERs, but did not substantially alter the conclusions from the MS.

Schering-Plough submission[92]

Re-treating patients who did not respond or relapsed following previous interferon treatment was estimated to result in a QALY gain of 1.03, compared with supportive care, at an incremental cost of £4536, resulting in an ICER of £4387. These results were reported for a combined cohort of genotype 1 and 4 (84% of total) patients and genotype 2 and 3 patients. Separate results are also reported for the two genotype subgroups: the ICERs were £7177 per QALY gained for genotype 1 and 4 patients and £783 per QALY gained for genotype 2 and 3 patients. The submission also reports subgroup analyses (not stratified by genotype) for non-responding and relapsed patients separately – suggesting that the QALY gain is higher for relapsed than for non-responding patients. Effectiveness data for this group of patients were taken from the unpublished EPIC3 study,[96] which recruited patients who had been previously treated with non-peginterferon as well as peginterferon. The effectiveness data in the model appear not strictly to meet the scope issued by NICE, as they appear to be based on all patients in the EPIC3 study, not just those who were previously treated with peginterferon.

For a cohort of patients (of all genotypes) co-infected with HCV/HIV, treatment with peginterferon was estimated to result in a gain of 2.32 QALYs compared with no treatment, at an incremental cost of £2502, resulting in an ICER of £1077. For patients with genotypes 1 and 4 the ICER was estimated at £1637 per QALY gained, while for patients with genotypes 2 and 3 the ICER was £403 per QALY gained.

The DSA showed that the ICERs in both the re-treated and the co-infected cohorts were sensitive to variation in the EVR and SVR, and to changes in patient weight, as dosing of both peginterferon alfa-2b and ribavirin are weight based. In the re-treatment group ICERs showed a small increase in response to changes in disease severity distribution within the patient group.

Probabilistic sensitivity analyses were conducted including the majority of parameters in the model. The choice of distribution applied to parameters appears to have been appropriate. Three PSAs are reported for each patient group (re-treated and HCV/HIV co-infected patients) – the first is for the overall cohort of patients followed by separate analyses for genotype subgroups. The PSA reports high probability (> 90%) of treatment with peginterferon alfa-2b being cost-effective for all analyses, at willingness-to-pay thresholds of £20,000 and £30,000.

Independent economic assessment

We adapted a previously published model[17] to undertake an independent economic assessment of shortened treatment duration with peginterferon alfa, based on SVRs extracted from clinical trials included in our clinical effectiveness review. Our economic model was structurally similar

to those developed by the manufacturers, using similar input parameters to model disease progression, health-state costs and utility. The model consists of nine non-absorbing health states representing stages of chronic liver disease and one absorbing state representing death. The model has a cycle length of 1 year and incorporates a half-cycle adjustment.

Baseline populations in the model were based on a clinical audit undertaken at a London teaching hospital, differentiating between new and existing patients in terms of average age and the distribution of patients across stages of chronic liver disease.[101] The proportion of men in the baseline cohort was based on our previous assessment.

For the subgroup of genotype 1 patients with baseline LVL and who achieve an RVR, shorter duration of treatment with peginterferon alfa-2a (from 48 to 24 weeks) reduced total costs by approximately one-third (approximately £5000) but was also associated with slightly poorer outcome (4%–6% lower SVR, resulting in a reduction in total QALYs of 0.08 to 0.14). The ICERs were positive (as both incremental cost and incremental QALYs are negative) and range from around £35,000 per incremental QALY to £65,000 per incremental QALY. As these ICERs are derived as a ratio of two negative values, the commonly assumed decision rule – Is the ICER below a given threshold? – does not hold. In this situation the logic is reversed and ICERs below the threshold are rejected. This can be better understood using the net benefits framework.

Shorter duration of treatment with peginterferon alfa-2a (from 24 to 16 weeks) for genotype 2 and 3 patients reduced total costs by approximately one-quarter (between £2000 and £3000) and was associated with better outcome in the included trials (2%–7% higher SVR, resulting in an increase in total QALYs of 0.08 to 0.23). In these scenarios, shortened treatment duration dominated standard care for the subgroup of genotype 2 or 3 patients with baseline LVL and who achieve an RVR.

For genotype 1 patients with baseline LVL and who achieve an RVR, shorter duration of treatment with peginterferon alfa-2b (from 48 to 24 weeks) reduced total costs by approximately one-third (approximately £9000), and was associated with better outcome in the included trial [15% higher SVR (8/19 vs 16/28), resulting in an increase in total QALYs of 0.49]. This results in shortened treatment with peginterferon alfa-2b dominating standard duration of treatment for this patient group.

No RCTs of re-treatment of patients previously treated with peginterferon, or of treatment in patients with HCV/HIV co-infection, met the inclusion criteria for our review of clinical effectiveness. The analyses of these patient subgroups have used data that have not been formally quality assessed in the same way as for the review of shortened treatment duration.

For peginterferon alfa-2a, the analysis of re-treatment of patients who did not respond to previous peginterferon therapy, and was based on data included in the submission by Roche,[104] provided further detail on the trial reported by Jensen and colleagues.[88] In this analysis, re-treatment using peginterferon alfa-2a resulted in increased costs and increased QALYs. The ICER for genotype 1 patients was £52,587 per QALY gained, and for genotype non-1 patients was £10,926 per QALY gained. The ICERs changed marginally when accounting for patients withdrawing from treatment owing to adverse events. Adopting an early stopping rule based on EVR led to a substantial reduction in incremental costs for treated patients. The ICERs for each group reduced to £9169 per QALY gained in genotype 1 and £2294 per QALY gained in genotype non-1.

For peginterferon alfa-2b, the analysis of re-treatment of patients who did not respond to previous peginterferon therapy was based on data included in the submission by

Schering-Plough[92] reporting evidence from the EPIC3 study.[96] In this analysis, re-treating patients with genotypes 1 and 4 increased costs by £9380, and increased QALYs by 0.39, resulting in an ICER of £23,912. For genotypes 2 and 3, these costs were reduced by £989 and QALYs increased by 1.72, resulting in peginterferon alfa-2b dominating BSC. Adopting an early stopping rule based on EVR led to a substantial reduction in incremental costs for treated patients. The ICERs for the group including genotypes 1 and 4 patients reduced to £7681 per QALY gained.

For patients who were co-infected with HCV/HIV, treatment with peginterferon alfa-2a resulted in a QALY gain of 0.75 for genotypes 1 and 4, and 1.86 for genotypes 2 and 3. Costs also increased by approximately 27% (£5932) in genotypes 1 and 4, which resulted in a positive ICER of £7941 per QALY gained in this group. Costs decreased overall as a result of treating genotypes 2 and 3 by approximately 8%, a reduction of £1717. This resulted in peginterferon alfa-2a dominating BSC in this group of patients.

For patients who are co-infected with HCV/HIV, treatment with peginterferon alfa-2b resulted in increased costs for both genotypes 1 and 4 and genotypes 2 and 3 (£7901 and £2989, respectively). The QALY gain also increased by 0.67 and 1.38, respectively. ICERs for both groups were positive: in genotypes 1 and 4 this was £11,806 per QALY gained, and in genotypes 2 and 3 it was £2161 per QALY gained.

Summary of cost-effectiveness evidence

All three models used in this assessment (the two manufacturers' models and the independent model adopted by the assessment group) were structurally similar and used similar parameter inputs for the chronic HCV natural history model. However, there were key differences in structural assumptions regarding the SVR state, health-state utility and characteristics of the baseline cohorts entering the models that led to differences in cost-effectiveness results.

For patients co-infected with HCV/HIV, and in patients who did not respond to previous peginterferon alfa combination therapy, the cost-effectiveness results are broadly consistent, but with less favourable ICERs in the independent economic assessment. For the subgroup of patients who were eligible for shortened duration of treatment, the results of the manufacturer's analysis and the independent economic assessment are inconsistent. In the manufacturer's analysis, shortened duration of treatment would not be a cost-effective treatment option at conventionally accepted threshold values, whereas in the independent economic assessment shortened treatment duration would be a cost-effective option. The difference in the results of these analyses arises from the differences in structural assumptions, health-state utility and baseline cohort characteristics, as well as differences in effectiveness data used in the two models. The interpretation of the ICER results is complicated by the fact that shortened duration of treatment would most typically be associated with a QALY loss (compared with standard duration) owing to a reduction in effectiveness (lower SVR). Interpretation of such cost-saving and QALY-reducing options can be aided by adopting the net benefits approach, rather than relying on ICERs.

Strengths and limitations of the assessment

- In terms of strengths, this technology assessment report has been undertaken following standard principles for conducting a systematic review.[49] The methods were set out in a research protocol that defined the research question, inclusion criteria, quality criteria, data extraction process and methods to be used at different stages of the review (see *Appendix 1*).

An advisory group has informed the review from its initiation. The research protocol was informed by comments received from the advisory group, and the advisory group has reviewed and commented on the final report.

- The report brings together the evidence for the clinical effectiveness and cost-effectiveness of peginterferon alfa and ribavirin for chronic HCV in three specific patient groups. This evidence has been critically appraised and presented in a consistent and transparent manner.
- An economic model has been developed following recognised guidelines, and systematic searches have been conducted to identify data for the economic model. The main results have been summarised and presented. The report is also independent of any vested interest.
- In terms of limitations it should be acknowledged that outcome data, in terms of SVR according to RVR and LVL, in the studies evaluating shortened courses of treatment, were based on patient subgroups as opposed to all randomised patients. It is unlikely that the RCTs were statistically powered with respect to these subgroups so caution is advised in the interpretation of data.

Two of the RCTs of peginterferon alfa-2a included in our systematic review of clinical effectiveness used doses of ribavirin according to body weight, which is no longer within the licence indication. Both of these trials restricted inclusion to genotype 2[55] or genotype 2/3 patients.[56] The product licence for peginterferon alfa-2a specifies that ribavirin should be given in a fixed dose of 800 mg to patients with genotypes 2 and 3. Both trials appear to have been designed and executed before the licence variation. Exclusion of these RCTs solely on this basis would have further reduced the evidence base in our systematic review such that there would be no evidence of the impact of shortened treatment durations in patients with genotypes 2 or 3.

The majority of studies used to derive estimates of response to treatment with peginterferon alfa did not make the comparisons specified by NICE. For re-treatment of patients who did not respond or relapsed following previous treatment and also patients with HCV/HIV co-infection the specified comparator was supportive care, while the clinical trials have active comparators. We were unable to construct evidence networks that included placebo (or supportive care) controlled trials. As a result, in common with the manufacturers, we have conducted the comparison with supportive care by assuming that the spontaneous SVR rate will be zero. While this is generally supported by clinical opinion, it remains an assumption and is not supported by robust evidence.

Parameters in the model (disease progression, utility and health-state cost) have not been derived for the specific patient subgroups in this assessment. Targeted searches undertaken for this review did not identify suitable data, for the relevant patient groups, for the majority of parameters in the model. It is not clear how applicable health-state utility values for HCV mono-infected patients are to those with HCV/HIV co-infection. Similarly, treatment costs based on protocols for mono-infected patients may underestimate the resource use required for on-treatment management of HCV/HIV co-infected patients. We have attempted to address this through sensitivity analyses.

In common with our previous technology assessment reports,[17,44] we have presented the results of this report separately for peginterferon alfa-2a and alfa-2b, as these agents are generally considered to be pharmacologically distinct from each other. It should be acknowledged that one of the RCTs included in the systematic review of clinical effectiveness, Mangia and colleagues,[52] treated patients with either peginterferon alfa-2a or -2b in both of its arms, as opposed to the other RCTs, each of which evaluated either alfa-2a or alfa-2b but not both in the same trial.

Uncertainties

Across the included trials, RVR and LVL were not consistently defined, with the lower limits of detection of the virus being different between studies. RVR was defined as undetectable serum HCV RNA but the lower threshold for detection varied from < 25 to < 615 IU/ml. Similarly, the threshold for LVL differed between trials with a cut-off HCV RNA level of < 400,000 or < 800,000 IU/ml being used to differentiate between low and high viral load. This variability in cut-off limits has implications for the number of patients rightly classified as having LVL or achieving an RVR. In clinical practice, an HCV RNA < 30 IU/ml at week 4 of treatment is generally regarded as an RVR.

Sustained virological response has not been reported according to stage of liver disease in the included studies. However, peginterferon alfa treatment is indicated for patients with compensated liver disease and is therefore likely to be provided to patients with compensated cirrhosis. Fibrosis stage (particularly cirrhosis) has been shown consistently (in other populations of patients with chronic HCV) to be associated with poorer outcome in terms of SVR. We have attempted to address this by including sensitivity analyses adopting a lower probability of SVR in patients with cirrhosis.

Quality of life/health-state utility weights in the model were taken from reports on a multicentre trial, which recruited treatment-naive patients with mild HCV and this was supplemented by an observational study recruiting patients with compensated and decompensated cirrhosis. It is not clear how applicable these QoL weights are to some of the subgroups of patients in the current assessment – re-treated patients are likely to be older while QoL assessments for mono-infected patients may not be directly applicable to those with HCV/HIV co-infection. Similarly, the health-state costs included in the model were developed in an observational study conducted alongside the UK Mild Hepatitis C Trial,[81,82] whereas intervention costs were based on treatment protocols developed as part of our previous assessment[17] in collaboration with UK clinical experts, and valued using reference costs from an NHS Hospital Trust. It is not clear how adequately the treatment protocols may capture the complexity of managing patients with HCV/HIV co-infection – the sensitivity of the cost-effectiveness results to the costs of managing antiviral treatment in this group of patients was addressed in a sensitivity analysis.

There is very limited information on the baseline characteristics of patients undergoing treatment for chronic HCV. We found no information on characteristics for patients in the relevant subgroups and have used baseline characteristics from our previous assessment and a small audit undertaken in a London teaching hospital. Clinical experts for this review regarded these assumptions as reasonable, but this remains an assumption and is not supported by robust evidence.

Chapter 8

Conclusions

Implications for service provision

A recommendation to extend antiviral treatment to patients who did not respond to, or who relapsed from, a previous course of peginterferon alfa and ribavirin combination therapy may increase the number of eligible patients in some areas, with resultant budget implications for primary care trusts and increased use of hepatology services.

For patients co-infected with HCV/HIV, there would be implications for the availability of resources and a need for HIV specialists to work closely with hepatitis specialists. The complexity of this joint management is probably achievable in many tertiary centres but may pose some difficulties for isolated centres. Furthermore, the reality of provision of joint clinics, and other aspects of joint management, could pose significant logistical challenges for service managers, particularly if the dominance of one disease specialist in a patient's care is to be avoided and a more holistic approach adopted.

Suggested research priorities

Further RCTs are required to assess the clinical effectiveness of re-treating people who have not responded to, or have relapsed following, a previous course of peginterferon alfa. Trials of new pharmacological agents should be conducted, particularly for patients in whom re-treatment with a subsequent course of peginterferon alfa is not successful in terms of achieving undetectable levels of virus. It is important to increase the number of treatment options for this group, as currently there are no other licensed agents available. Phase II and III trials are currently in progress, evaluating the safety and efficacy of protease inhibitors for chronic HCV, which can be used in combination with peginterferon alfa in both treatment-naive and treatment-experienced patients, such as telaprevir and boceprevir. In Phase III development is the nucleoside analogue taribavirin (a prodrug of ribavirin), which is being evaluated for use in combination with peginterferon alfa. Also being trialled is albinterferon alfa-2b, a genetic fusion of human albumin and interferon, which can be administered via injection every 2 weeks, in contrast to peginterferon alfa, which is given once a week. New agents such as these, once licensed, may be eligible for appraisal by NICE so that guidance can be issued to the NHS on their use.

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Contribution of authors

D Hartwell (Research Fellow) developed the research protocol, contributed to the background section, assisted in the development of the search strategy, assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, drafted and edited the final report, and project managed the study.

J Jones (Principal Research Fellow) developed the research protocol, assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, developed the economic evaluation and drafted the report.

L Baxter (Research Fellow) assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, assisted in developing the economic evaluation and drafted the report.

J Shepherd (Principal Research Fellow) contributed to developing the research protocol, drafted the background section, assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence and drafted the report.

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Appendix 1

Methods from research protocol

Title of the project

Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (part review of TA75 and TA106).

Report methods for synthesis of evidence of clinical effectiveness

A review of the evidence for clinical effectiveness and cost-effectiveness will be undertaken systematically following the general principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care.[49]

Search strategy

A search strategy will be developed and tested by an experienced information scientist. The strategy will be designed to identify: (1) clinical effectiveness studies reporting on comparisons between peginterferon and ribavirin combination therapy (or peginterferon monotherapy for those who cannot tolerate ribavirin) and best supportive care (BSC) or standard-duration courses of peginterferon/ribavirin (as described in *Inclusion and exclusion criteria*); and (2) studies reporting on the cost-effectiveness of peginterferon and ribavirin, and the relative comparisons. The search strategy will also identify studies reporting resource use and costs, epidemiology and natural history.

The following electronic databases will be searched: the Cochrane Library, including the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL); Centre for Reviews and Dissemination (CRD, University of York); Database of Abstracts of Reviews of Effects (DARE); the NHS Economic Evaluation Database (NHS EED); the Health Technology Assessment (HTA) database; MEDLINE (Ovid); EMBASE (Ovid); PREMEDLINE In-Process & Other Non-Indexed Citations (Ovid); Web of Science with Conference Proceedings: Science Citation Index Expanded (SCIE) and Conference Proceedings Citation Index – Science (CPCI-S) (ISI Web of Knowledge); Biosis Previews (ISI Web of Knowledge); NIHR-Clinical Research Network Portfolio; ClinicalTrials.gov; and Current Controlled Trials. Relevant hepatitis C symposia will also be searched. The draft search strategy for MEDLINE will be adapted for other databases.

Bibliographies of related papers will be assessed for relevant studies where possible. The manufacturers' submissions to the National Institute for Health and Clinical Excellence (NICE) will be assessed for any additional studies that meet the inclusion criteria. Experts will be contacted to identify additional published and unpublished evidence.

Literature searches will be carried out from April 2007 (the date the most recent search was conducted[48] to the present and will be limited to randomised controlled trials (RCTs) and the English language (note: the search will incorporate the references identified in our previous technology assessment reports[17,44] in which literature searching extended back to the year 2000;

these references will be rescreened according to the inclusion criteria for the current assessment). For the cost-effectiveness assessment, searches for other evidence to inform cost-effectiveness modelling will be conducted as required and may include a wider range of study types (including non-randomised studies). All searches will be updated when the draft report is under review, prior to submission of the final report.

Inclusion and exclusion criteria

The following criteria are those stipulated in the final scope issued by NICE.[61]

Population

Adults with chronic hepatitis C virus (HCV) infection, restricted to:

- people who have been previously treated with peginterferon alfa and ribavirin in combination but who relapsed/did not respond
- people who meet the criteria within the marketing authorisation for receiving shortened courses of peginterferon alfa and ribavirin in combination, namely:
  - patients with genotype 2 or 3 with a low viral load (LVL) at the start of treatment and a rapid viral response (defined as HCV RNA undetectable by week 4)*
  - patients with genotype 1 with a LVL and a rapid viral response (defined as HCV RNA undetectable by week 4 and at week 24)
  - patients with genotype 4 and a rapid viral response
- people with HCV/HIV co-infection.

The subgroups are not mutually exclusive.

(*Applies only to peginterferon alfa-2a.)

Intervention

- Combination therapy comprising ribavirin and either peginterferon alfa-2a or peginterferon alfa-2b.
- Peginterferon alfa-2a or peginterferon alfa-2b monotherapy (for patients who are unable to tolerate or are contraindicated to ribavirin).

Comparators

For patients who have been previously treated with combination therapy, and for HCV/HIV co-infected patients:

- Best supportive care (e.g. symptomatic treatment, monitoring, treatment without any form of interferon therapy).

For patients who meet the criteria for receiving shortened courses of combination therapy:

- Standard duration courses of peginterferon alfa and ribavirin combination therapy (up to 24 or 48 weeks as appropriate).

Outcomes

Studies must report sustained virological response (SVR) (defined as undetectable HCV RNA at least 6 months after treatment cessation). Studies may also include one or more of the following outcomes:

- virological response (e.g. during treatment, end of treatment)
- biochemical response [e.g. alanine aminotransferase (ALT) levels]

- histological improvement (fibrosis and inflammation)
- survival
- adverse effects of treatment
- health-related quality of life (QoL)
- cost-effectiveness [incremental cost per quality-adjusted life-year (QALY)].

Types of studies

- Fully published RCTs will be included.
- Studies published as abstracts or conference presentations from 2007 onwards will be included only if sufficient details are presented to allow an appraisal of the methodology and the assessment of results to be undertaken.
- For the systematic review of cost-effectiveness, studies will only be included if they report the results of full economic evaluations [cost-effectiveness analyses (reporting cost per life-year gained), cost–utility analyses or cost–benefit analyses].
- Systematic reviews will only be used as a source of references.
- Case series, case studies, narrative reviews, editorials and opinions will not be included.
- Non-English language studies will be excluded.

Screening and data extraction process

Reference screening

The titles and abstracts of studies identified by the search strategy will be assessed for potential eligibility using the inclusion/exclusion criteria detailed above. This will be performed by one reviewer. Full papers of studies that appear potentially relevant will be requested for further assessment, and these will be screened by one reviewer and checked by a second. Any disagreements will be resolved by discussion, with involvement of a third reviewer where necessary.

Data extraction

Data will be extracted by one reviewer using a standardised data extraction form. Extracted data will be checked by a second reviewer. Discrepancies will be resolved by discussion, with recourse to a third reviewer when necessary.

Quality assessment strategy

The quality of the clinical effectiveness studies will be assessed according to criteria based on that used by the CRD (University of York).[49] Economic evaluations will be assessed using criteria recommended by Drummond and colleagues[67] and/or the format recommended and applied in the CRD NHS Economic Evaluation Database (NHS EED) (using principles outlined in the NHS EED Handbook[106]). For any studies based on decision models we will also make use of the checklist for assessing good practice in decision analytic modelling (Philips and colleagues[69]). Published studies carried out from the UK NHS and Personal and Social Services (PSS) perspective will be examined in more detail.

The quality of the individual studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus, and if necessary a third reviewer will be consulted.

Methods of data analysis/synthesis of clinical effectiveness data

Clinical effectiveness data will be synthesised through a narrative review with tabulation of the results of included studies. Where data are of sufficient quality and homogeneity, a meta-analysis of the clinical effectiveness studies will be performed to estimate a summary measure of effect on relevant outcomes. If a meta-analysis is appropriate, it will be performed using Cochrane Review

Manager (REVMAN 5) software. Where data allow, clinical effectiveness and cost-effectiveness will be assessed according to patient subgroups (e.g. by genotype, baseline viral load).

Methods for synthesising evidence of cost-effectiveness

Published and submitted economic evaluations

Narrative synthesis, supported by the data extraction tables, will be used to summarise the evidence base from published economic evaluations. Any economic evaluation included in sponsor submissions to NICE will be assessed using the same quality criteria as for published economic evaluations, but will be reported separately.

Economic modelling

Where appropriate, an economic model will be constructed by adapting an existing model or developing a new one using best available evidence. The Markov model developed by the Southampton Health Technology Assessments Centre (SHTAC) for a previous NICE assessment of treatment for mild chronic hepatitis C[17] will be reviewed to assess its applicability to the patient subgroups within the scope of the current review. If the model structure is considered appropriate, the model will be further reviewed to determine whether updated parameter estimates for disease progression, health-state utility or resource use/cost are required. All updated parameter estimates will be derived from the best available published literature, NHS sources (including Finance Department at Southampton University Hospitals Trust) and industry submissions, where applicable.

The perspective for the analysis will be that of the NHS and PSS. The incremental cost-effectiveness of the interventions will be estimated in terms of cost per QALY gained, as well as the cost per life-year gained if data permit. Both cost and outcomes will be discounted at 3.5%.

Parameter values for the model will be obtained from relevant research literature, including our own systematic review of clinical effectiveness. Where required parameters are not available from good-quality published studies in the relevant patient group, we may use data from sponsor submissions to NICE or experts' clinical opinion. Searches for additional information regarding model parameters, patient preferences and other topics will be conducted as required. Sources for parameters will be stated clearly.

Resource use will be specified and valued from the perspective of the NHS and PSS. Cost data will be derived from local sources, extracted from published sources or from sponsor submissions to NICE, as appropriate.

The simulated population will be defined on the basis of the published evidence about the characteristics of UK chronic HCV patients, within the scope of the current review, and the populations for which good-quality clinical effectiveness is available. The base-case results will be presented separately for the subgroups of patients:

- who have been previously treated with peginterferon alfa and ribavirin in combination and did not respond or responded but relapsed
- who meet the licensed criteria for receiving shortened courses of combination therapy
- with HCV/HIV co-infection.

The time horizon for our analysis will initially be governed by the outcomes reported, and the follow-up data available from included clinical trials – we will investigate the feasibility of extrapolating treatment effects beyond the clinical trials.

Methods for estimating QoL

Where presented, QoL information as well as incidence of adverse events and side effects of treatment will be extracted from included RCTs. Adverse effects of treatment that are likely to have a substantial impact on patients' QoL, will be included in estimates of health-state utility while on treatment. Where QoL data are insufficient to calculate utility estimates, data will be derived from the broader literature or estimated from other sources. Ideally, utility values will be taken from studies that have been based on 'public' (as opposed to patient or clinician) preferences elicited using a choice-based method (in accordance with NICE methodological guidance).[68]

Analysis of uncertainty

Analysis of uncertainty will focus on cost–utility, assuming the cost per QALY can be estimated. Uncertainty will be explored through one-way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented both using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs).

Handling the company submission(s)

All data submitted by the manufacturers will be considered if received by the technolgoy assessment report (TAR) team no later than 27 August 2009. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's guidance on presentation,[68] will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model.

Methods adopted, and incremental cost-effectiveness ratios (ICERs) estimated from models supporting the company submission will be compared with published economic evaluations of peginterferon and ribavirin included in the assessment report and with the results from the Assessment Group's analysis. Reasons for large discrepancies in estimated ICERs will be explored and, where possible, explained.

Any 'academic-in-confidence' data or 'commercial-in-confidence' data taken from a company submission will be underlined and highlighted in the assessment report.

Appendix 2

Search strategies

The following strategies were used to search MEDLINE (Ovid) and EMBASE (Ovid) 2007–9 (searches from the previous assessment reports[17,44] covered the period 2000–7). The strategies were translated to search the other databases listed in *Chapter 3* (*Identification of studies*).

Clinical effectiveness searches

MEDLINE (Ovid)

1. (hepatitis c or HCV).mp. (35,528)
2. exp Hepatitis C/ (26,263)
3. Hepatitis C, Chronic/ (9982)
4. Hepacivirus/ (12,474)
5. or/1-4 (35,757)
6. Ribavirin/ (4279)
7. (ribavirin or copegus or rebetol).ti,ab,nm. (5452)
8. (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. (15,918)
9. Interferon Alfa-2a/ (2560)
10. Interferon Alfa-2b/ (3487)
11. Polyethylene Glycols/ (13,117)
12. 11 and (9 or 10) (1364)
13. 6 or 7 or 8 or 12 (19,230)
14. 5 and 13 (4722)
15. limit 14 to (english language and humans and yr="2007 - 2009") (1144)
16. (systematic$adj2 review$).mp. (18,692)
17. (systematic$adj2 overview$).mp. (354)
18. meta-analysis/ (18,478)
19. (meta analysis or metaanalysis).ab,pt,ti. (25398)
20. randomized controlled trial.pt. (172,423)
21. Randomized Controlled Trial/ (172,423)
22. random allocation/ (29,335)
23. random*.ti,ab. (310,605)
24. controlled clinical trial.pt. (33,195)
25. Controlled Clinical Trial/ (33,195)
26. randomized controlled trials/ (51,594)
27. Single-Blind Method/ (10,146)
28. Double-Blind Method/ (55,762)
29. ((singl$or doubl$or tripl$or trebl$) adj5 (blind$or mask$)).tw. (53,879)
30. exp placebos/ (9753)
31. placebo*.ti,ab. (69,682)
32. exp research design/ (154,706)
33. or/16-32 (520,197)
34. 15 and 33 (233)
35. (letter or comment or editorial).pt. (551,934)
36. 34 not 35 (225)

37. from 36 keep 1-222 (222)

(222 in search on 20 May 2009; re-ran for strategy on 2 June 2009 – extra three results)

Added in interferon terms on 2 June 2009:

38. 38 interferon alpha/ (8733)
39. (interferon alpha or interferon alfa or roferon or intron or viraferon).ti,ab. (27,829)
40. 5 and (38 or 39) (4209)
41. limit 40 to (english language and humans and yr="2007 - 2009") (520)
42. 41 not 36 (438)
43. 33 and 42 (6)
44. exp interferon alpha/ (13,975)
45. 5 and (39 or 44) (5932)
46. limit 45 to (english language and humans) (5023)
47. 33 and 46 (999)
48. limit 47 to yr="2007 - 2009" (207)
49. (letter or comment or editorial).pt. (551,934)
50. 48 not 49 (198)
51. 50 not 36 (9)
52. from 36 keep 1-3 (3)
53. 51 or 52 (12)
54. from 53 keep 1-12 (12)

EMBASE (Ovid)

1. (hepatitis C or hcv).mp. (40,260)
2. exp Hepatitis C/or exp Hepatitis C virus/ (37,333)
3. 1 or 2 (40,260)
4. (peginterferon$or peg-ifn or peg-interferon$or (peg$adj3 interferon$) or (polyethylene glycol adj3 interferon$) or Pegasys or pegintron or viraferonpeg).mp. (5786)
5. peginterferon/or peginterferon alpha2a/or peginterferon alpha2b/ (5285)
6. (interferon alpha or interferon alfa or roferon or intron or viraferon).ti,ab. (25,587)
7. exp Alpha Interferon/ (21,113)
8. Recombinant Alpha2a Interferon/ (1749)
9. Recombinant Alpha2b Interferon/ (2660)
10. interferon/or alpha2a interferon/or alpha2b interferon/or alpha interferon/ (36,974)
11. or/4-10 (58,971)
12. 3 and 11 (12,123)
13. limit 12 to (human and english language and yr="2007 - 2009") (2516)
14. (systematic$adj2 review$).mp. (35,802)
15. (systematic$adj2 overview$).mp. (341)
16. (meta analy$or metaanaly$).ti,ab,pt. (21,234)
17. exp meta analysis/ (31,882)
18. randomized controlled trial/ (139,490)
19. controlled clinical trial/ (61,251)
20. exp randomization/ (24,841)
21. exp double blind procedure/ (53,393)
22. exp single blind procedure/ (7234)
23. placebo*.tw. (70,462)
24. random*.tw. (295,710)
25. ((singl$or doubl$or tripl$or trebl$) adj5 (blind$or mask$)).tw. (55,235)
26. ((hand or manual or computer or electronic or database) adj2 search*).ti,ab. (8649)
27. or/14-26 (410,504)
28. 13 and 27 (337)
29. (comment or editorial or letter).pt. (305,933)

30. 28 not 29 (334)
31. from 30 keep 1-334 (334)

Cost-effectiveness searches

MEDLINE (Ovid)

1. "hepatitis C" or HCV).mp. (35,682)
2. exp hepatitis C/or Hepatitis C, Chronic/or exp Hepacivirus/ (29,926)
3. or/1-2 (35,914)
4. exp "Costs and Cost Analysis"/ (82,109)
5. exp Cost–benefit Analysis/ (30,108)
6. exp health care costs/ (26,090)
7. Economics, Medical/or Economics, Pharmaceutical/ (2298)
8. (pharmacoeconomic* or pharma economic*).tw. (1724)
9. (cost$adj2 (benefit* or utilit* or minim*)).tw. (9235)
10. (decision adj1 (tree* or analys* or model*)).tw. (3934)
11. Markov Chains/ (4817)
12. Monte Carlo Method/ (10,228)
13. or/4-12 (102,814)
14. 3 and 13 (486)
15. limit 14 to (english language and humans and yr="2007 - 2009") (76)
16. Ribavirin/ (4308)
17. (ribavirin or copegus or rebetol).ti,ab,nm. (5488)
18. (peginterferon$or peg-ifn or peg-interferon$or (pegylat$adj3 interferon$) or peg$or (polyethylene glycol adj3 interferon$) or ViraferonPeg or pegintron or Pegasys).mp. (16,012)
19. Interferon Alfa-2a/ (2577)
20. Interferon Alfa-2b/ (3506)
21. Polyethylene Glycols/ (13,172)
22. 21 and (19 or 20) (1379)
23. ((interferon adj1 alpha) or (interferon adj1 alfa)).ti,ab. (11,238)
24. (roferon or intron or viraferon).ti,ab. (18,563)
25. hepatitis c/dt (2820)
26. hepatitis c chronic/dt (4565)
27. or/16-18,22-26 (49,445)
28. 15 and 27 (29)

EMBASE (Ovid)

1. (hepatitis C or hcv).mp. (40,384)
2. exp Hepatitis C/or exp Hepatitis C virus/ (37,440)
3. 1 or 2 (40,384)
4. (peginterferon$or peg-ifn or peg-interferon$or (peg$adj3 interferon$) or (polyethylene glycol adj3 interferon$) or Pegasys or pegintron or viraferonpeg).mp. (5811)
5. peginterferon/or peginterferon alpha2a/or peginterferon alpha2b/ (5299)
6. (interferon alpha or interferon alfa or roferon or intron or viraferon).ti,ab. (25,641)
7. exp Alpha Interferon/ (21,178)
8. Recombinant Alpha2a Interferon/ (1751)
9. Recombinant Alpha2b Interferon/ (2663)
10. interferon/or alpha2a interferon/or alpha2b interferon/or alpha interferon/ (37,087)
11. or/4-10 (59,136)
12. 3 and 11 (12,158)
13. *Economics/ (449)

14. monte carlo method/ (7621)
15. markov.ti,ab. (4291)
16. cost minimization analysis/ (1493)
17. cost of illness/ (5027)
18. cost utility analysis/ (2561)
19. drug cost/ (30,500)
20. economic evaluation/ (4615)
21. pharmacoeconomics/ (870)
22. budget/ (6833)
23. "resource use".ti,ab. (2058)
24. (cost or economic*).ti. (27,489)
25. *health economics/ (2099)
26. *health care cost/ (7402)
27. or/13-26 (81,064)
28. 12 and 27 (326)
29. (cost and effective* and "hepatitis C").ti. (101)
30. (cost and effective* and "hepatitis C").ab. (312)
31. 11 and (29 or 30) (188)
32. 28 or 31 (391)
33. limit 32 to (human and english language and yr="2007 - 2009") (66)
34. (letter or editorial).pt. (489,386)
35. 33 not 34 (63)

Quality of life searches

MEDLINE (Ovid)

1. value of life/ (1918)
2. quality adjusted life year/ (3675)
3. quality adjusted life.ti,ab. (2613)
4. (qaly$or qald$or qale$or qtime$).ti,ab. (2126)
5. disability adjusted life.ti,ab. (515)
6. daly$.ti,ab. (520)
7. health status indicators/ (10,595)
8. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (8391)
9. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (400)
10. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab. (1125)
11. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. (5)
12. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab. (164)
13. (euroqol or euro qol or eq5d or eq 5d).ti,ab. (1471)
14. (hql or hqol or h qol or hrqol or hr qol).ti,ab. (3294)
15. (hye or hyes).ti,ab. (20)
16. health$year$equivalent$.ti,ab. (14)
17. health utilit$.ab. (502)
18. (hui or hui1 or hui2 or hui3).ti,ab. (417)
19. disutil$.ti,ab. (86)

20. rosser.ti,ab. (35)
21. quality of well being.ti,ab. (169)
22. quality of wellbeing.ti,ab. (1)
23. qwb.ti,ab. (99)
24. willingness to pay.ti,ab. (973)
25. standard gamble$.ti,ab. (448)
26. time trade off.ti,ab. (378)
27. time tradeoff.ti,ab. (150)
28. tto.ti,ab. (282)
29. (index adj2 well being).mp. (261)
30. (quality adj2 well being).mp. (468)
31. (health adj3 utilitind).mp. (381)
32. ((multiattribute$or multi attribute$) adj3 (health ind$or theor$or health state$or utilit$or analys$)).mp. (109)
33. quality adjusted life year$.mp. (4680)
34. (15D or 15 dimension$).mp. (705)
35. (12D or 12 dimension$).mp. (152)
36. rating scale$.mp. (37,389)
37. linear scal$.mp. (292)
38. linear analog$.mp. (349)
39. visual analog$.mp. (14,997)
40. (categor$adj2 scal$).mp. (595)
41. or/1-40 (81,641)
42. (letter or editorial or comment).pt. (556,056)
43. 41 not 42 (79,235)
44. (hepatitis C or hcv).mp. (35,792)
45. exp Hepatitis C/or Hepatitis C, Chronic/or exp Hepacivirus/ (30,013)
46. 43 and (44 or 45) (311)
47. limit 46 to (english language and humans and yr="2007 - 2009") (72)
48. "quality of life".ti. (19,254)
49. ("hepatitis C" or HCV or "hepacivurs").ti. (22,969)
50. 48 and 49 (100)
51. limit 50 to (english language and humans and yr="2007 - 2009") (26)
52. 47 or 51 (80)

EMBASE (Ovid)

1. quality adjusted life year/ (4254)
2. quality adjusted life.ti,ab. (2661)
3. (qaly$or qald$or qale$or qtime$).ti,ab. (2184)
4. disability adjusted life.ti,ab. (472)
5. daly*.ti,ab. (482)
6. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (8281)
7. (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. (498)
8. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab. (1055)
9. (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. (3)
10. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab. (145)

11. (euroqol or "euro qol" or "eq5d" or "eq 5d").ti,ab. (1485)
12. (hql or hqol or "h qol" or hrqol or "hr qol").ti,ab. (3251)
13. ("hye" or "hyes").ti,ab. (16)
14. health* year* equivalent*.ti,ab. (16)
15. health utilit*.ti,ab. (525)
16. (hui or hui1 or hui2 or hui3).ti,ab. (378)
17. disutil*.ti,ab. (82)
18. rosser.ti,ab. (31)
19. quality of well being.ti,ab. (161)
20. quality of wellbeing.ti,ab. (5)
21. qwb.ti,ab. (98)
22. willingness to pay.ti,ab. (970)
23. standard gamble*.ti,ab. (430)
24. time trade off.ti,ab. (387)
25. time tradeoff.ti,ab. (140)
26. tto.ti,ab. (299)
27. (index adj2 well being).mp. (258)
28. (quality adj2 well being).mp. (453)
29. (health adj3 util* adj ind*).mp. (389)
30. ((multiattribute* or multi attribute*) adj3 (health ind* or theor* or health state* or util* or analys*)).mp. (112)
31. quality adjusted life year*.mp. (4976)
32. health status indicator*.ti,ab. (95)
33. (15D or 15 dimension*).mp. (737)
34. (12D or 12 dimension*).mp. (160)
35. "health related quality of living".ti,ab. (2)
36. "health related quality of life".ti,ab. (9742)
37. rating scale*.mp. (58,665)
38. visual analog*.mp. (19,195)
39. (categor* adj scale*).mp. (255)
40. linear scal*.mp. (214)
41. linear analog*.mp. (345)
42. or/1-41 (97,590)
43. (editorial or letter or comment).pt. (491,976)
44. 42 not 43 (94,514)
45. exp hepatitis C/or exp hepacivirus/ (37,643)
46. ("Hepatitis C" or HCV).mp. (40,598)
47. 44 and (45 or 46) (434)
48. limit 47 to (human and english language and yr="2007 -Current") (111)
49. ("quality of life" and (HCV or Hepatitis C or hepacivirus)).ti. (102)
50. limit 49 to (human and english language and yr="2007 -Current") (27)
51. 48 or 50 (115)
52. from 51 keep 1-115 (115)

Epidemiology searches

MEDLINE (Ovid)

1. *Hepatitis C, Chronic/ep
2. ("hepatitis C" adj4 (incidence or prevalence or epidemiolog* or "natural history")).ti,ab.
3. ((natural* or disease*) adj4 (progres* or course* or histor*)).ti,ab.
4. hepatitis C chronic/

5. 3 and 4
6. 2 and chronic.ti,ab.
7. 1 or 5 or 6
8. limit 7 to (english language and humans and yr="2007 - 2009")

EMBASE (Ovid)

1. ("hepatitis C" and (epidemiolog* or incidence or prevalence or statistic*)).ti.
2. limit 1 to (human and english language and yr="2007 - 2009")

EMBASE (Ovid) – strategy specifically relating to HCV/HIV co-infection

1. coinfection.tw.
2. co?infection*.tw.
3. (hiv and (hepatitis C or HCV)).ti,ab.
4. 3 and (1 or 2)
5. (incidence or prevalence or epidemiol* or "natural history" or rate*).tw.
6. 4 and 5
7. limit 6 to (english language and humans and yr="2005 - 2006")
8. (mortality or morbidity).tw.
9. 4 and 8
10. 7 or 9
11. limit 10 to (human and english language and yr="2005 - 2006")
12. (co?infection* adj5 (incidence or prevalence or epidemiol* or "natural history" or mortality or morbidy)).tw.
13. 3 and 12
14. limit 13 to (human and english language and yr="2005 - 2006")
15. ("hepatitis C" adj5 (incidence or prevalence or epidemiol* or "natural history" or mortality or morbidity or survival)).tw.
16. (HCV adj5 (incidence or prevalence or epidemiol* or "natural history" or mortality or morbidity or survival)).tw.
17. 15 or 16
18. limit 17 to (human and english language and yr="2005 - 2006")
19. ("hepatitis C" or HCV).ti.
20. 18 and 19
21. chronic.ti,ab.
22. 20 and 21
23. *hepatitis C/ep [Epidemiology]
24. (chronic adj2 "hepatitis C").ti,ab.
25. 23 and 24
26. ("chronic hepatitis C" or "chronic HCV").ti.
27. (incidence or prevalence or epidemiol* or "natural history" or mortality or morbidity or survival).ti.
28. 26 and 27
29. limit 28 to (human and english language and yr="2005 - 2006")
30. 14 or 29
31. ("chronic hepatitis C" or "chronic HCV").ab.
32. 27 and 31
33. limit 32 to (human and english language and yr="2005 - 2006")
34. 30 or 33
35. risk factor*.ti,ab.
36. 26 and 35
37. limit 36 to (human and english language and yr="2005 - 2006")
38. 34 or 37

Additional searching

All references of the five included trials were checked to ensure that no eligible studies had been missed.

Appendix 3

SHTAC peer review of clinical effectiveness in the manufacturers' submissions of peginterferon and ribavirin for chronic hepatitis C

Roche hepatitis C submission to NICE 2009

Summary

- Manufacturer's submission (MS) does not present itself as a systematic review.
- Manufacturer reports a simple EMBASE search using what appear to be free-text terms. No search results presented (in terms of number of hits screened, etc.).
- No explicit inclusion criteria are used except 'When possible predominantly data from prospective, randomised, active control studies with good statistical power and similar to UK patient population were considered' (p. 28). There is no evidence of any systematic process for applying this rule.
- With the exception of some uncontrolled studies, all of the trials included had active comparators and for the re-treatment and HCV/HIV co-infection patient groups this contravenes the scope of the NICE appraisal.
- There is no mention of the possibility of conducting an indirect comparison with no active treatment for the re-treatment and HCV/HIV co-infection patient groups.
- A number of retrospective subgroup analyses are included, some of which appear to have been funded by Roche (and published), and some which are 'data on file'.
- Of the six RCTs currently included in the SHTAC systematic review of clinical effectiveness, only two have been included by Roche.

Re-treatment studies

Study included in MS		Eligible for inclusion in the current SHTAC systematic review of clinical effectiveness?	Study details	Comments
MV17150 REPEAT study, Jensen and colleagues (2009)[88]		No	In total, 942 patients treated, all non-responders to prior PEG	Active comparator study (different induction doses/lengths of PEG)
			Four-arm trial: PEG α-2a, 360 µg/week, for 12 weeks then 180 µg/week to complete 72 weeks (group A) or 48 weeks (group B); or PEG α-2a, 180 µg/week for 72 weeks (group C) or 48 weeks (group D)	In the economic model, SVRs are used from a subgroup of non-responders from this study (data on file)
HALT-C (lead-in phase)	Shiffman and colleagues (2004)[107]	No	Reports first 604 patients entering lead-in phase of HALT-C	The majority of patients in HALT-C were non-responders to IFN monotherapy (24%) or IFN–RBV combination therapy (66%); this contravenes the scope of the NICE appraisal
	Everson and colleagues (2006)[108]		Described as an updated publication data set used as part of the European Medicines Agency filing in February 2008	
			Reports 1046 patients who had RNA assessments at weeks 20 and 72; analyses results in four subgroups of patients subdivided by increasing liver disease severity	
	Shiffman and colleagues (2007)[109]		Subgroup of 936 gastrointestinal patients with RNA assessments at weeks 20 and 72 (a subgroup of the 1046 in Everson and colleagues[108])	
WV16143, Berg and colleagues (2006)[89]		No	Described as a 'supporting study'	Uncontrolled
			Uncontrolled trial in 64 patients. Patients had originally been in the NV15942 trial by Hadziyannis and colleagues (2004),[91] but had relapsed	
Yoshida and colleagues (2009)[110]		No	Described as a 'supporting study'	
			Post hoc analysis of a Canadian, multicentre, open-label study	
			87 non-responders/relapsers	
Parise and colleagues (2006)[111]		No	Described as a 'supporting study'	
			134 Brazilian relapsers/non-responders to non-PEG/RBV	

IFN, interferon; MS, manufacturer's submission; PEG, peginterferon; RBV, ribavirin.

Shorter courses studies: genotypes 2 and 3

Study included in MS		Eligible for inclusion in the current SHTAC systematic review of clinical effectiveness?	Study details	Comments
ACCELERATE NV17317	Shiffman and colleagues (2007)[90]	No	1469 patients 16 vs 24 weeks of PEG + RBV 31% of patients had LVL at baseline (≤ 800,000 IU/ml)	Paper was excluded from TAR because SVRs were not presented for patients with LVL and RVR SVRs from this trial are used in manufacturer's economic model
	Retrospective analysis Zeuzem and colleagues (2005)[112]	No	Mentions a retrospective research report 1026369, which reports results for patients with a RVR and LVL 216 patients with RVR and LVL in 16-week arm, 200 patients with RVR and LVL in 24-week arm	Attributes this retrospective analysis to Zeuzem *et al.*[112] Manufacturer uses SVRs from this study in their economic model (89% for 16-week group vs 94% for 24-week group) These SVRs are similar to those used in the von Wagner and colleagues[56] and Yu and colleagues[55] studies below
von Wagner and colleagues (2005)[56]		Yes	Both studies described as 'supportive' evidence in the submission. Mentions that both used unlicensed weight-based RBV doses for genotype 2/3 (hence why not included in their main analysis)	von Wagner and colleagues[56] RBV dose = 800/1000/1200 mg
Yu and colleagues (2007)[55]		Yes		Yu and colleagues[55] RBV dose = 1000/1200 mg

IU, international unit; PEG, peginterferon; RBV, ribavirin.

Shorter courses studies: genotype 1

Study included in MS	Eligible for inclusion in the current SHTAC systematic review of clinical effectiveness?	Details	Comments
Jensen and colleagues (2006)[113]	No	Retrospective analysis based on the one-third of genotype 1 patients who achieved an SVR after 24 weeks' treatment in the Hadziyannis trial[91] (incorrectly referred to as 2006 on p. 97 of submission) Purpose was to assess factors associated with RVR and an SVR in genotype 1 patients treated for 24 weeks	SVRs from this study are used in manufacturer's economic model
Ferenci and colleagues (2005)[114]	No	Retrospective analysis of data from an RCT of 48 weeks' PEG + RBV treatment in 1121 patients (compared with IFN + RBV)	

IFN, interferon; PEG, peginterferon; RBV, ribavirin.
There is no mention of the Liu and colleagues[53,57] or the Yu and colleagues'[55] genotype 1 studies included in the SHTAC TAR.

Shorter courses studies: genotype 4

Study included in MS	Eligible for inclusion in the current SHTAC systematic review of clinical effectiveness?	Details	Comments
Ferenci and colleagues (2008)[115]	No	Retrospective analysis of NV15801 (Jensen and colleagues 2006) and NV 15942 (Hadziyannis trial[91]) Note: On p. 106 they refer to this as being a Research Report 1023045 data on file, and refer to the clinical trials as NV15801 (Fried and colleagues[41]) and NV 15942 (Yu and colleagues[54]). There is some confusion here regarding the identity of the trials	Study was excluded from our review because it is not a randomised comparison of 24 vs 48 weeks. Patients with RVR were treated for 24 weeks, those without were then randomised at weeks 12–48 or 72 weeks. The journal paper presents SVRs for only the 24-week group anyway (ongoing trial)

HCV/HIV co-infection

Study included in MS	Eligible for inclusion in the current SHTAC systematic review of clinical effectiveness?	Details	Comments
APRICOT Torriani and colleagues (2004)[66]	No	868 treatment-naive co-infected patients randomised to receive: PEG α-2a (180 µg/week) plus RBV (800 mg per day); PEG α-2a plus placebo, or IFN α-2a (3 million IU three times/week) plus RBV	
Laguno and colleagues (2009)[94]	No	Prospective multicentre RCT in Spain; compares PEG α-2a with PEG α-2b	Described in the MS as a 'supporting study'

IFN α, interferon alfa; PEG α, peginterferon alfa; RBV, ribavirin.

Schering-Plough hepatitis C submission to NICE 2009

- Manufacturer's submission only covers the re-treatment and HCV/HIV co-infection patient groups of the appraisal, not the shortened courses patient group (no explanation given for this).
- Submission describes itself as a 'systematic review' conducted for the company's own use as well as for NICE, so therefore it considers evidence beyond the scope of the appraisal including trials with active comparators (though for the purposes of the appraisal it does not use all of the trial arms). Although it provides details of its search strategy it does not describe the methods for screening and data extracting studies. Not clear on what basis they selected studies other than they were ones that were 'pivotal' in their licence extension application.

Re-treatment studies

Study included in MS	Eligible for inclusion in the current SHTAC systematic review of clinical effectiveness?	Details	Comments
EPIC3 study (clinical study report on file), P02370, P02569, P02570	No	Short-term non-randomised uncontrolled efficacy phase (P02370) followed by long-term maintenance stage (PEG mono vs no treatment) to prevent disease progression (P02569 and P02570) Submission presents short-term results of first efficacy cohort Patients re-treated after failing previous IFN + RBV or PEG + RBV Data from this trial are used in their economic evaluation: genotypes 1 and 4 EVR/SVR = 29.76%/48.65%; genotypes 2 and 3 = 79.13% and 69.95%, respectively	Similar trial to HALT-C, but uses PEG α-2b
Scotto and colleagues (2008)[97]	No	RCT PEG α-2a + RBV vs PEG α-2b + RBV for 48 weeks in previous IFN + RBV non-responders	Does not meet scope of the appraisal as patients are not re-treated following PEG

IFN, interferon; PEG, peginterferon; RBV, ribavirin.

HCV/HIV co-infection

Study included in MS	Eligible for inclusion in the current SHTAC systematic review of clinical effectiveness?	Details	Comments
P01017 (Carrat and colleagues 2004,[116] Pol and colleagues 2005[117])	No	RCT PEG α-2b + RBV vs IFN + RBV	Active comparator studies, not within scope of appraisal
P02080 (Laguno and colleagues 2004[95])	No	RCT PEG α-2b + RBV vs IFN + RBV Efficacy estimates from this trial used in their economic evaluation: genotypes 1 and 4 = 38%; genotypes 2 and 3 = 53%	
Laguno and colleagues (2009)[94]	No	RCT PEG α-2a + RBV vs PEG α-2b + RBV Efficacy estimates from this trial used in sensitivity analysis	

IFN, interferon; PEG α, peginterferon alfa; RBV, ribavirin.

Appendix 4

Inclusion criteria worksheet for systematic review of clinical effectiveness

Trial name or number				
Design: RCT or systematic review Exclude any conference abstracts from 2006 or earlier	Yes ↓ Next question	Unclear ↓ Next question	No → EXCLUDE	EXCLUDE1 (E1) (not the appropriate study design)
Population: Adult patients with chronic hepatitis C, restricted to one or more of the following groups: ■ re-treated following previous relapse or non-response to PEG and RBV (or PEG monotherapy) ■ HCV/HIV co-infected ■ eligible for shortened course of treatment *(Note: Can be mild/moderate or severe hepatitis C)*	Yes ↓ Next question	Unclear ↓ Next question	No → EXCLUDE	EXCLUDE2 (E2) (not the appropriate patient group)
Intervention: Patients re-treated following previous relapse or non-response to PEG and RBV (or PEG monotherapy, and/or HIV/HCV co-infected) 1. PEG + RBV 2. PEG monotherapy *Compared with BSC/placebo* **Intervention:** (Patients eligible for shortened course of treatment): ■ genotype 2/3 patients with LVL and RVR, shorten tx from 24 to 16 weeks (PEG α-2a only) ■ genotype 1 patients with LVL and RVR, shorten tx from 48 to 24 weeks (PEG α-2a or α-2b) ■ genotype 4 patients with RVR, shorten tx from 48 to 24 weeks (PEG α-2a only) 1. PEG + RBV 2. PEG monotherapy *Compared with 'standard' duration courses of PEG/RBV (up to 24 or 48 weeks as appropriate)*	Yes ↓ Next question	Unclear ↓ Next question	No → EXCLUDE	EXCLUDE3 (E3) (not the appropriate intervention)
Outcomes: SVR, defined as undetectable HCV RNA for at least 6 months after treatment cessation	Yes ↓ Next question	Unclear ↓ Next question	No → EXCLUDE	EXCLUDE4 (E4) (not the appropriate outcome measures)
Final decision	**INCLUDE**	**UNCLEAR (Discuss)**	**EXCLUDE**	**Results of discussion:**

LVL, low viral load (≤ 800,000 IU/ml PEG α-2a; ≤ 600,000 IU/ml PEG α-2b); PEG, peginterferon; RBV, ribavirin; RVR, rapid virological response [HCV RNA undetectable at week 4 (genotype 2/3); HCV RNA undetectable at week 4 and 24 (genotype 1/4)]; tx, treatment.

Appendix 5

Quality assessment criteria

CRD criteria for assessment of risk of bias in RCTs[49]

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

Appendix 6

Data extraction forms and critical appraisal

Berg and colleagues[59]

Reviewer 1: JS 16 November 2009, reviewer 2: DH 16 November 2009

Reference and design	Intervention	Participants	Outcome measures
Author: Berg and colleagues[59] *Year*: 2009 *Study design*: Open-label, multicentre RCT *No. of centres*: 19 *Country*: Germany *Sponsor*: Essex Pharma (subsidiary of Schering-Plough), Bayer diagnostics, German Competence Network for Viral Hepatitis (German Ministry of Education and Research)	**Group 1: standard treatment duration** *n* = 225 *Drug 1*: PEG α-2b Dose: 1.5 µg/kg/week Duration: 48 weeks *Drug 2*: RBV Dose: 800–1400 mg/day Duration: 48 weeks **Group 2: variable treatment duration** *n* = 208 *Drug 1*: PEG α-2b Dose: 1.5 µg/kg/week Duration: 18, 24, 30, 36, 42 or 48 weeks[a] *Drug 2*: RBV Dose: 800–1400 mg/day Duration: 18, 24, 30, 36, 42 or 48 weeks[a]	**Total numbers involved:** 438 patients screened, 433 randomised **Treatment naive/non-responders/relapsers**: Treatment naive **Previous treatment**: NA **HCV/HIV co-infection**: No **Recruitment**: December 2001 and July 2003 **Inclusion criteria:** 18–70 years, compensated chronic HCV genotype 1, previously untreated with any type of IFN alfa and/or RBV, anti-HCV positive, HCV RNA > 1000 IU/ml by quantitative reverse-transcription PCR, increased serum ALT levels at screening, liver biopsy within preceding 24 months confirming chronic hepatitis, neutrophil count ≥ 1500/l and platelet count ≥ 80,000 l, Hb ≥ 12 g/dl for females and ≥ 13 g/dl for males, creatinine levels < 1.5 mg/dl **Exclusion criteria:** Patients with HCV type other than type 1, decompensated liver disease, hepatitis B or HIV co-infection or other causes of liver disease, autoimmune disorders, concomitant immunosuppressive medication, clinically significant bleeding disorders, clinically significant cardiac or cardiovascular abnormalities, organ grafts, systemic infections, pre-existing severe psychiatric conditions, evidence of malignant neoplastic diseases, excessive daily intake of alcohol (≥ 40 g/day in women and ≥ 60 g/day in men), drug abuse within past year, or unwillingness to practice contraception ***Baseline measurements:*** **Viral load log (IU/ml), mean ± SD** Group 1: 5.7 ± 0.49, range 2.79–7.8 Group 2: 5.7 ± 0.45, range 3–7.6 **Serum ALT × ULN (IU/l), mean ± SD** Group 1: 2.6 ± 0.2, range 0.5–28.8 Group 2: 2.6 ± 0.4, range 0.4–1.6 **Histology**: *Fibrosis stage 0–2, n (%)*[b]: Group 1: 177 (87%) Group 2: 161 (85.1%) *Fibrosis stage 3–4, n (%)*[b]: Group 1: 34 (13%) Group 2: 31 (14.9%) **Necroinflammatory score, mean (± SD):** NR **Genotypes, *n* (%):** 1 (100)	**Primary outcomes:** SVR **Secondary outcomes:** Sustained biochemical response (ALT normalisation at end of follow-up) On-treatment virological response rates (RVR and EOT) Relapse rate Adverse events **Length of follow-up:** 24 weeks after cessation of treatment **Methods of assessing outcomes:** HCV RNA levels were quantified at baseline and weekly until week 8 as well as at weeks 12, 24 and 48 by bDNA assay (detection limit 615 IU/ml) SVR HCV RNA negativity verified using highly sensitive qualitative TMA assay (detection limit < 5.3 IU/ml). This assay was reserved only for those patients who had HCV RNA levels of < 1000 IU/ml by the bDNA test. The cut-off of 1000 IU/ml, instead of 615 IU/ml, was chosen to improve the specificity of the bDNA assay. Patients with HCV RNA levels of between 615 and 1000 IU/ml but being HCV RNA negative on TMA were considered bDNA undetectable after confirmation by re-testing HCV genotyping performed by reverse hybridisation; histological results classified using standard criteria (Desmet 1994 cited)

Reviewer 1: JS 16 November 2009, reviewer 2: DH 16 November 2009

Reference and design	Intervention	Participants	Outcome measures
		Gender male, *n* (%): Group 1: 128 (57) Group 2: 113 (54.3) **Age (years), mean ± SD, range:** Group 1: 42.8 ± 0.8, 18–73 Group 2: 42.7 ± 11.69, 19 –66 **Ethnic groups, *n* (%):** NR **Mode of infection, *n* (%):** NR **Losses to follow-up, *n* (%):** Group 1: Therapy and follow-up completed 150 (67) Therapy completed 154 (68) Follow-up completed 189 (84) Group 2: Therapy and follow-up completed 135 (65) Therapy completed 145 (70) Follow-up completed 174 (84) **Compliance, *n*:** *Therapy discontinuations (n = 71)* Group 1: Therapy failure 39 Adverse events 7 Lost to follow-up 24 Other reason 1 *Therapy discontinuations (n = 63)* Group 2: Therapy failure 42 Adverse events 4 Lost to follow-up 15 Other reason 2	

HVL, high viral load (> 800,000 IU/ml); LVL, low viral load (≤ 800,000 IU/ml); PEG α, peginterferon alfa; RBV, ribavirin; RVR, rapid virological response (defined as HCV RNA negativity < 615 IU/ml at week 4); SVR, sustained virological response [defined as negative qualitative HCV RNA (< 5.3 IU/ml by sensitive TMA assay) 24 weeks after the end of treatment].

a Individualised duration based on time to first HCV RNA negativity by bDNA assay multiplied by a factor of 6. First negative at week 3, 4, 5, 6, 7 or 8 corresponded to a treatment duration of 18, 24, 30, 36, 42 or 48 weeks, respectively ($n = 28$ appear to have been treated for 24 weeks).

b It is not clear from the trial publication what the denominators were for these percentages. The percentages given are not for the total randomised in each study group. It therefore does not appear that all patients randomised underwent liver biopsy at baseline.

Treatment failures:

Breakthrough (reappearance of HCV viraemia during antiviral treatment); relapse (reappearance of HCV RNA during follow-up after stopping therapy in patients with an EOT virological response) or non-response (patients testing HCV RNA positive at any time point during the study).

Outcome	Group 1 standard ($n=225$), (48 weeks)	Group 2 variable ($n=208$), (18–48 weeks)	p-value
Viral response, % (n/N), 95% CI:			
4-week (RVR)[c]	8.4[d] (19/225)	13.5[d] (28/208)	NR
RVR (weeks 1–3 + week 4)[e]	35[d] (78/225)	37[d] (76/208)	NR
12-week (EVR)	–	–	
End of treatment	65 (146/225) 58.3 to 71.1	64 (133/208) 57 to 70.5	NR
End of follow-up (SVR)	48 (108/225) 41.3 to 54.7	35 (72/208) 28.2 to 41.5	0.005
SVR by RVR, % (n/N)[f]	42 (8/19)	57 (16/28)	NR
SVR by baseline viral load, % (n/N)	–	–	–
SVR by baseline viral load and RVR, % (n/N)[g]			
≤ 800,000 IU/ml (low)	75 (3/4)	69 (11/16)	NR
> 800,000 IU/ml (high)	33 (5/15)	42 (5/12)	NR
Non-response % (n/N), 95% CI	18 (41/225) 13.4 to 23.9	20 (41/208) 14.5 to 25.8	NR
Virological relapse % (n/N), 95% CI	14 (32/225) 9.9 to 19.5	33 (68/208) 26.4 to 39.5	< 0.0005
Breakthrough % (n/N), 95% CI	5 (11/225) 2.5 to 8.6	3 (7/208) 1.4 to 6.8	NR

c Time to first HCV RNA < 615 IU/ml at week 4 by bDNA assay (not including those who became first negative between weeks 1 and 3).
d Percentage calculated by reviewer from numbers presented in trial publication.
e Total number of patients first becoming HCV RNA negative between weeks 1 and 3 ($n=59$ in Group 1, $n=48$ in Group 2) and those becoming first negative at week 4 ($n=19$ in Group 1, $n=28$ in Group 2) combined to give total number of patients becoming HCV RNA negative by week 4.
f Numerator calculated by reviewer from figures presented in trial publication.
g Study defines LVL as ≤ 800,000 IU/ml and HVL as > 800,000 IU/ml – this threshold for LVL is higher than the threshold of < 600,000 IU/ml specified in the SPC for PEG α-2b.

Biochemical response, % (n/N):	NR		
End of treatment			
End of follow-up			
Histology (proportion with improvement)	NR		
Adverse events:			
Dose discontinuation for any adverse event	3% (7/225)	2% (4/208)	
Dose reduction for any adverse event or lab abnormality	16%	15%	
Serious adverse events	6.6%: Anaemia $n=1$, appendectomy $n=1$, sinusitis $n=1$, pneumonia $n=2$, psychiatric disorder $n=7$, subileus $n=1$, wound infection $n=1$	2.6%: Ankle fracture $n=1$, retina ablation $n=1$, pneumonia $n=2$, psychiatric disorder $n=1$	0.243

Additional results/comments

Authors report that percentage of patients reporting adverse events was similar in the two treatment groups. Both the type and severity of treatment side effects (typical of IFN-based treatment) were not statistically different between the two groups (data not shown)

Most commonly observed causes of dose modifications of PEG α-2a and RBV were neutropenia and anaemia, respectively

Results (in terms of SVR by RVR, and SVR by RVR and baseline viral load) are also presented according to time to HCV RNA negativity as measured by the TMA assay (< 5.3 IU/ml). The purpose was to explore differences in treatment effect between the two assays. However, the SVRs according to TMA negativity at week 4 (i.e. RVR) in Group 2 are based on some patients who only received 18 weeks' treatment rather than 24 weeks' treatment. Treatment for less than 24 weeks in patients with genotype 1 (as a comparator to 48 weeks' treatment) is not within the scope of this systematic review and therefore the results have not been extracted here

Methodological comments

Allocation to treatment groups: Randomised by stratification for baseline viraemia (≤800,000 vs >800,000 IU/ml). No further detail given on randomisation procedure

Allocation concealment: No details given

Blinding: No details given, but due to the differences in regimens it is unlikely that patient or investigator blinding would be possible. No mention is made about whether outcome assessors (e.g. liver biopsy pathologists) were blinded to treatment allocation

Analysis by ITT: States that an ITT analysis was conducted, although does not provide a definition of what ITT considered to be. Patients were classified as unknown with respect to treatment response in the case of missing relevant data for exact and reliable categorisation

Comparability of treatment groups at baseline: Authors report that treatment groups were well matched and differed only slightly with respect to relevant variables by univariate between-group analyses (although statistics not presented)

Method of data analysis: Descriptive statistics used for all relevant dependent variables including absolute and relative frequencies for categorical data and means, standard deviations and ranges for continuous scaled data. Statistical comparisons between the two treatment groups were made using the chi-squared test. Multiple logistic regression was used to analyse the influence of independent predictive factors on the occurrence of an SVR

Sample size/power analysis: Study was originally designed to be a non-inferiority trial. An SVR of approximately 45% was estimated for the standard fixed duration of 48 weeks. A difference in SVR rates of up to 12.5% across both study arms was considered as still being equivalent. Under this assumption 436 patients were required if a level of significance of $\alpha = 0.05$, a minimal power of 80% and a drop out rate of 10% are assumed. Because there was a significantly higher SVR rate in the standard treatment arm (Group 1) the trial was switched to a superiority trial in accordance with guidance from the European Medicines Agency

Attrition/dropout: Rates of therapy and follow-up completion were 150 (67%) in Group 1 and 135 (65%) in Group 2

General comments

Generalisability: Results applicable to treatment-naive European genotype 1 patients with mild-to-moderate HCV-related fibrosis. Mean baseline viral load was low ($\log_{10}$ 5.7 = 501,187 IU/ml)

Intercentre variability: NR

Conflict of interests: NR

Quality criteria for assessment (updated CRD guidance)[a]

1.	Was the method used to generate random allocations adequate?	Unclear
2.	Was the allocation adequately concealed?	Unclear
3.	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes
4.	Were outcome assessors blinded to the treatment allocation?	Unclear
5.	Was the care provider blinded?	No
6.	Was the patient blinded?	No
7.	Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No
8.	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes
9.	Did the analysis include an ITT analysis?	Yes
	If so, was this appropriate?	Unclear
	If so, were appropriate methods used to account for missing data?	Unclear

a Answer: yes/no/unclear.

Mangia and colleagues[52]

Reference and design	Intervention	Participants	Outcome measures
Author: Mangia and colleagues[52] *Year*: 2008 *Study design*: Multicentre RCT *No. of centres*: 11 *Country*: Italy *Sponsor*: NR (but states no support was received from pharmaceutical companies)	**Intervention 1: standard group (48 weeks)** *n* = 237 *Drug 1*: PEG α-2a or α-2b Dose: α-2a 180 µg/week; α-2b 1.5 µg/kg/week Duration: 48 weeks *Drug 2*: RBV Dose: 1000 mg/day for patients ≤ 75 kg, 1200 mg/day for patients > 75 kg Duration: 48 weeks **Intervention 2: variable group (24, 48 or 72 weeks[a])** *n* = 459 *Drug 1*: PEG α-2a or α-2b Dose: α-2a 180 µg/week; α-2b 1.5 µg/kg/week Duration: 24, 48 or 72 weeks[a] *Drug 2*: RBV Dose: 1000 mg/day for patients ≤ 75 kg, 1200 mg/day for patients > 75 kg Duration: 24, 48 or 72 weeks[a]	**Total numbers involved:** 711 enrolled, 696 randomised; *n* = 237 Group 1, *n* = 459 Group 2 **Treatment naive/non-responders/relapsers:** Treatment naive **Previous treatment:** NA **HCV/HIV co-infection:** No **Recruitment:** 11 centres in southern Italy between June 2004 and December 2005 **Inclusion criteria:** Previously untreated adults (18–70 years) with compensated chronic HCV genotype 1, anti-HCV positive, HCV RNA positive, neutrophil count ≥ 1500 µl, platelet count ≥ 90,000 µl, Hb ≥ 12 g/dl for women and ≥ 13g/dl for men, creatinine < 1.5 mg/dl **Exclusion criteria:** Other causes of liver disease, hepatitis B, HIV, autoimmune disorders, clinically significant cardiac or cardiovascular abnormalities, systemic infection, organ graft, clinically significant bleeding disorders, evidence of malignant diseases, concomitant immunosuppressive medication, excessive alcohol intake or concomitant drug abuse, pregnancy, lactation or male partners of pregnant women ***Baseline measurements***: **Serum HCV RNA, *n* (%):** < 400,000 IU/ml: 62 (26%) Group 1, 103 (22%) Group 2, *p* = 0.30 ≥ 400,000 IU/ml: 175 (74%) Group 1, 356 (78%) Group 2 *Serum ALT, n (%)*: < 3 ULN: 193 (81%) Group 1, 385 (84%) Group 2, *p* = 0.39 ≥ 3 ULN: 44 (19%) Group 1, 74 (16%) Group 2	**Primary outcomes:** SVR **Secondary outcomes:** SVR according to virological response at weeks 4, 8 and 12 RVR EOT Adverse events **Length of follow-up:** 24 weeks after cessation of treatment **Methods of assessing outcomes:** HCV-RNA levels quantified at baseline (lower limit of detection 600 IU/ml) and qualitatively analysed by PCR assay (lower limit of detection 50 IU/ml) during and off therapy; HCV RNA of 400,000 IU/ml chosen as cut-off for LVL or high viral load. HCV genotyping performed by reverse hybridisation, histological results classified using standard criteria (Desmet cited); platelet counts < 140,000/mm^3 were taken as evidence of advanced fibrosis in patients without biopsy as per cited literature

Reference and design	Intervention	Participants	Outcome measures
		Histology: *Fibrosis stage, n (%):*[b] 0–2: 140 (62%) Group 1, 258 (65%) Group 2, $p=0.33$ 3–4: 87 (38%) Group 1, 134 (34%) Group 2 *Grade of activity, n (%):*[c] 0–2: 167 (76%) Group 1, 306 (78%) Group 2, $p=0.42$ 3: 54 (24%) Group 1, 89 (22%) Group 2 *Steatosis:*[d] Yes: 70 (31%) Group 1, 103 (26%) Group 2, $p=0.07$ No: 151 (68%) Group 1, 295 (74%) Group 2 **Genotypes, *n* (%):** 1a: 15 (6%) Group 1, 49 (11%) Group 2, $p=0.08$ 1b: 222 (94%) Group 1, 410 (89%) Group 2 **Gender, *n* (%):** Female: 105 (44%) Group 1, 201 (44%) Group 2, $p=0.93$ Male: 132 (56%) Group 1, 258 (56%) Group 2 **Age (years), mean (± SD):** 52.6 (± 11.8) Group 1, 51.1 (± 12.1) Group 2, $p=0.12$ **Ethnic groups, *n* (%):** NR **Mode of infection, *n* (%):** Blood transfusion: 50 (21%) Group 1, 93 (20%) Group 2 Drug abuse: 17 (7%) Group 1, 37 (8%) Group 2, $p=0.81$ Unknown: 170 (72%) Group 1, 329 (72%) Group 2 **Treatment, *n* (%):** PEG α-2b: 127 (53%) Group 1, 235 (51%) Group 2, $p=0.52$ PEG α-2a: 110 (46%) Group 1, 224 (49%) Group 2 **Losses to follow-up:** $n=6$ (Group 2) **Compliance:** $n=83$ (12%) discontinued treatment (24 Group 1, 59 Group 2) due to adverse events (16 Group 1, 30 Group 2) or no compliance (8 Group 1, 29 Group 2)	

EOT, end-of-treatment virological response; PEG α, peginterferon alfa; RBV, ribavirin; RVR, rapid virological response (defined as HCV RNA negative at week 4); SVR, sustained virological response (defined as undetectable serum HCV RNA at the end of 24 weeks' follow-up); ULN, upper limit of normal.
'Non-responders' defined as patients who were viraemic at week 24 and also patients with a < 2-log decline at week 12.
'Treatment failures' defined as relapse (reappearance of HCV RNA during follow-up period after an EOT response), non-response or discontinuation.

a Treatment duration was based on time when HCV RNA first became undetectable; patients who were first HCV RNA negative at: week 4 treated for 24 weeks, week 8 treated for 48 weeks, week 12 treated for 72 weeks.
b Data unavailable from 67 patients (10 Group 1, 57 Group 2).
c Data unavailable from 78 patients (14 Group 1, 64 Group 2).
d Data missing from 67 patients (6 Group 1, 61 Group 2).

Outcome	Group 1 standard ($n=237$), 48 weeks	Group 2 variable ($n=123$), 24 weeks	p-value
Note: Data have been extracted only for Group 1 vs 24-week subset of Group 2, as results for Group 2 as a whole ($n=459$) are not relevant to this review.			
Viral response, % (n/N, 95% CI):			
EOT by RVR	96.7 (60/62, 92.3 to 100)	95.1 (117/123, 92.3 to 99.4)	0.42
SVR by RVR	87.1 (54/62, 78.7 to 95.4)	77.2 (95/123, 69.8 to 84.6)	0.12; difference –9.9 (10.5 to 9.2)
SVR by RVR and baseline viral load, (n/N):			
≥ 400,000 IU/ml	86.8 (33/38)	73.1 (57/78)	0.14
< 400,000 IU/ml	83.3 (20/24)	84.4 (38/45)	0.83
Other viral response outcomes:			
Relapse rate (whole group), % (n/N)	19.1 (25/131)	19.4 (54/278)	1.0
Relapse rate by RVR, % (n/N)	10% (6/62)	18.8 (22/123) (Reviewer: should be 17.9.)	0.13
Biochemical response, % (n/N)	NR	NR	
Histology (proportion with improvement)	NR	NR	
Adverse events (for Group 1 vs Group 2, not 24-week subset of Group 2)	**Group 1, 48 weeks, $n=237$, n (%)**	**Group 2, 24, 48 or 72 weeks, $n=459$, n (%)**	
Dose discontinuation:	24 (10.1)	59 (12.9)	0.19
For any adverse event	16 (6.7)	30 (6.5)	
For no compliance	8 (3.4)	29 (6.3)	0.49
Dose reduction	32 (13.5)	47 (10.2)	
Specific adverse events, n (%):			
Asthenia	101 (42.6)	183 (39.8)	
Flu-like symptoms	34 (14.3)	87 (18.9)	
Dermatological symptoms	29 (12.2)	60 (13.0)	
Psychiatric symptoms	4 (1.7)	7 (1.5)	
Anaemia	20 (8.4)	33 (7.1)	
Leucopenia and thrombocytopenia	58 (24.4)	35 (7.6)	
Thyroid diseases	7 (2.9)	11 (2.3)	
Decrease in Hb to < 9.5 g/dl	20 (8.4)	33 (7.1)	0.66
Neutrophil count < 1000/mm^3 (requiring PEG dose reduction)	12 (5.1)	19 (4.1)	0.69

Additional results/comments (e.g. early response factors, QoL)

Virological response

Results for EOT, SVR and predictive factors were reported for Group 1 vs Group 2, as well as Group 1 vs the 48-week and 72-week subsets of Group 2, but these have not been extracted

In the entire population ($n=696$), 185 (26.6%) had undetectable HCV RNA at week 4 (i.e. RVR), comprising 62 (26.2%) Group 1 and 123 (26.8%) Group 2 (whole Group), $p=0.90$. An EOT response was achieved by 55.3% (131/237) and 60.6% (278/459) of the standard and variable treatment groups, respectively

RVR was achieved in 29% (105/362) patients treated with PEG α-2b and 24% (80/334) patients treated with PEG α-2a ($p=0.14$)

In univariate analysis (in entire population), factors associated with RVR were young age ($p=0.004$), low viraemia levels ($p=0.0001$) and fibrosis stage ≤ 2 ($p=0.0001$). In multivariate analysis (entire population), independent predictors of RVR were serum HCV RNA levels < 400,000 IU/ml [odds ratio (OR) 2.27, 95% CI 1.49 to 3.41] and absence of advanced fibrosis (OR 1.40, 95% CI 1.15 to 1.64)

The only independent predictor of SVR in RVR patients was a mild-to-moderate degree of fibrosis (OR 2.60, 95% CI 1.09 to 6.17). Off therapy, 24.4% of patients with high viraemia, and 8.9% of patients with low viraemia, relapsed ($p=0.05$)

Methodological comments

Allocation to treatment groups: Patients were allocated 1 : 2 in blocks of five, using a computer-generated randomisation list that was sent to each participating centre. PEG α-2a or α-2b was prescribed on a 1 : 1 basis

Allocation concealment: No details reported

Blinding: Blinding of participants and care providers not possible and blinding of outcome assessors not reported

Analysis by ITT: ITT analysis – all randomised patients who received at least one dose of study medication were used for analysis of primary and secondary outcomes

Comparability of treatment groups at baseline: Participant baseline demographic, biological and virological characteristics were well matched between Group 1 and Group 2, with no statistically significant differences (*p*-values reported). Also reports that baseline characteristics did not differ between patients treated with PEG α-2a and PEG α-2b (but data not presented). However, comparability of Group 1 (48 weeks) vs 24 weeks subset is unknown

Method of data analysis: The descriptive analysis included absolute and relative frequencies for grouped data and means ± SD for continuous scaled data. Statistical comparison between patients with and without SVR used the chi-squared test and the *t*-test (continuous data). Level of significance was 0.05 (two-sided) for all statistical tests; all CIs provided are at 95%. SPSS was used for statistical analysis

Sample size/power analysis: Study designed as a non-inferiority analysis comparing standard and variable treatment duration. An SVR rate of 45% was expected on the basis of data from previous cited international studies. Sample size of 212 patients per treatment group was estimated to show that the variable treatment duration is no more than 5% different than the standard duration, with one-sided 95% CI and 80% power. With a dropout rate of 10%, 237 patients per group were required. Given that the secondary aim of investigating SVR rates according to on-treatment virological response, double this number (474) of patients were assumed to be recruited into the variable group for meaningful subgroup comparisons. [*Important note*: Only 69 (9.9%) patients (24 Group 1, 45 Group 2 24-week subset) had LVL (< 400,000 IU/ml) and RVR and thus the study was likely not powered for this subgroup.]

Attrition/dropout: Numbers and reasons provided for those discontinuing treatment; numbers provided for those lost to follow-up. Numbers reported for those completing treatment are not consistent between figure 1 and table 3. Figure 1 reports 144 completed, 24 discontinued, 69 HCV RNA positive at week 24 (Group 1); 297 completed, 59 discontinued, 103 HCV RNA positive at week 24 (Group 2). Table 3 reports 122 completed treatment, 24 discontinued, 91 no response at week 24 (Group 1); 237 completed treatment, 59 discontinued, 163 no response at week 24 (Group 2)

General comments

Generalisability: Treatment-naive, Italian patients with genotype 1 HCV. Only 24% had LVL at baseline and only 10% had LVL and RVR

Intercentre variability: Reports that HCV RNA testing carried out at individual centres provided that all centres used the same assay. However, no intercentre variability reported. For better comparisons between different histopathologists, individual fibrosis stage was documented as significant (cirrhosis/transition to cirrhosis) or not significant (no cirrhosis)

Conflict of interests: None reported

Other: This is not a standard 48-week vs 24-week study in genotype 1 patients as Group 2 included patients treated for 24, 48 and 72 weeks, although some results were reported separately. Also, as noted above, only 10% of patients fulfilled the inclusion criteria of having LVL and RVR – the study was included because SVR rates were reported separately for this subgroup, but results should be treated with caution

Quality criteria for assessment (updated CRD guidance)[a]

1.	Was the method used to generate random allocations adequate?	Yes
2.	Was the allocation adequately concealed?	Unclear
3.	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes (Group 1 vs Group 2); unclear for Group 1 vs 24-week subset
4.	Were outcome assessors blinded to the treatment allocation?	Unclear
5.	Was the care provider blinded?	No
6.	Was the patient blinded?	No
7.	Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No
8.	Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
9.	Did the analysis include an ITT analysis?	Yes
	If so, was this appropriate?	Yes
	If so, were appropriate methods used to account for missing data?	Unclear

a Answer: yes/no/unclear.

Liu and colleagues[53]

Reference and design	Intervention	Participants	Outcome measures
Author: Liu and colleagues, Liu and colleagues (abstract)[53,57] *Year*: 2008, 2008 abstract *Study design*: Open-label, multicentre RCT *No. of centres*: 5 *Country*: Taiwan *Sponsor*: National Taiwan University Hospital, National Science Council, and Department of Health, Executive Yuan, Taiwan	**Group 1: 24 weeks** *n* = 154 *Drug 1*: PEG α-2a Dose: 180 g/week s.c. Duration: 24 weeks *Drug 2*: RBV Dose: 1000 mg/day for body weight < 75 kg and 1200 mg/day for body weight ≥ 75kg Duration: 24 weeks **Group 2: 48 weeks** *n* = 154 *Drug 1*: PEG α-2a Dose: 180 µg/week s.c. [a]Duration: 48 weeks *Drug 2*: RBV Dose: 1000 mg/day for body weight < 75 kg and 1200 mg/day for body weight ≥ 75kg Duration: 48 weeks	**Total numbers involved**: 308 patients *n* = 154 Group 1, *n* = 154 Group 2 **Treatment naive/non-responders/relapsers**: Treatment naive **Previous treatment**: NA **HCV/HIV co-infection**: No **Recruitment**: Five academic centres (in Taiwan hospitals) between June 2006 and March 2008 **Inclusion criteria**: Patients with genotype 1 aged > 18 years, presence of anti-HCV antibody and detectable serum HCV RNA level for > 6 months, serum ALT level > ULN, liver histological characteristics consistent with chronic viral hepatitis within the last 3 months **Exclusion criteria**: Anaemia: < 13 g/dl for men; < 12 g/dl for women, neutropenia (neutrophil count < 1500 cells/mm^3), thrombocytopenia (platelet count < 70,000 cells/mm^3), mixed infection with HCV-1 and another genotype of HCV, co-infection with hepatitis B virus or HIV, chronic alcohol abuse (daily alcohol consumption > 20 g/day), DC (Child–Pugh class B or C), serum creatinine level > 1.5 times the ULN, autoimmune liver disease, neoplastic disease, organ transplantation or immunosuppressive therapy, evidence of drug abuse, pregnancy, poorly controlled autoimmune disease, cardiopulmonary disease, neuropsychiatric disorders, diabetes mellitus with retinopathy, unwillingness to receive contraception during the study period **Baseline measurements**: *Viral load (IU/ml), mean log$_{10}$ (± SD)*: 5.7 ± 0.7 (Group 1), 5.8 ± 0.7 (Group 2), *p* = 0.83 *Serum ALT: mean value × ULN ± SD*: 3.2 ± 2.6 (Group 1), 3.0 ± 2.1 (Group 2), *p* = 0.91 **Histology**: *Fibrosis score n (%)*: ≥ 3: 121 (78.6) (Group 1), 117 (76.0) (Group 2), *p* = 0.68 6: 35 (22.7) (Group 1), 31 (20.1) (Group 2), *p* = 0.68 (≥ 3 = significant fibrosis, 6 = cirrhosis) *Mean total modified HAI score, (±SD)*: 12.7 ± 3.3 (Group 1), 12.3 ± 3.7 (Group 2), *p* = 0.43 **Genotypes, *n* (%):** 1a: 4 (2.6) Group 1, 3 (1.9) Group 2 1b: 143 (92.9) Group 1, 145 (94.2) Group 2 1a and 1b: 7 (4.5) Group 1, 6 (3.9) Group 2 **Gender male, *n* (%):** 88 (57.1) (Group 1), 87 (56.5) (Group 2), *p* > 0.99 **Age (years), mean (range):** 54 ± 10 (Group 1), 53 ± 11 (Group 2), *p* = 0.41	**Primary outcomes**: SVR rate **Secondary outcomes**: RVR EVR EOT virological response Relapse rate ALT normalisation Histological response **Length of follow-up:** Additional 24 weeks of follow-up after end of therapy **Methods of assessing outcomes:** Patients received outpatients visits to assess the efficacy and safety at weeks 1, 2, 4, 6 and 8 of the study and then monthly until the end of the follow-up period Serum HCV RNA levels quantitatively assessed at baseline, weeks 4, 12, end of treatment and 24 weeks after end of treatment (lower limit of detection 25 IU/ml). Patients in 48-week group had an additional HCV RNA test at week 24 of treatment Liver biopsies were performed at baseline and at the end of the follow-up period and assessed in accordance with Brunt's classification, and the modified HAI

Reference and design	Intervention	Participants	Outcome measures
		Ethnic groups, *n* (%): Asian (no further details reported) **Mode of infection, *n* (%):** NR **Losses to follow up:** Group 1: 7 discontinued prior to treatment completion, 0 after treatment completion Group 2: 4 discontinued prior to treatment completion, 15 after treatment completion **Compliance:** NR	

Complete EVR, an undetectable serum HCV RNA level at week 12 of therapy in patients who did not achieve RVR, and partial EVR was defined as at least a 2-log reduction in serum HCV RNA level from baseline to week 12 of therapy in those who did not achieve RVR at week 4 and did not achieve an undetectable serum HCV RNA level at week 12 of therapy; EVR, early virological response, defined as at least a 2 log reduction in serum HCV RNA level from baseline to week 12 of therapy.
ALT, alanine aminotransferase; DC, decompensated cirrhosis; EOT, virological response defined as an undetectable serum HCV RNA at the end of treatment; HAI, histological activity index; PEG α, peginterferon alfa; RBV, ribavirin; RVR, rapid virological response defined as an undetectable serum HCV RNA level (< 25 IU/ml) at week 4 of therapy; s.c., subcutaneously; SVR, an undetectable serum HCV RNA at the end of the follow-up period; histological response rate defined as at least two-point reduction in the modified histological activity index from baseline to follow up; relapse included patients with an undetectable HCV RNA level at the end of treatment but with a detectable level at the end of follow-up; ULN, upper limit of normal.
a Treatment was prematurely discontinued in patients who were randomised to 48 weeks of treatment but who continued to have HCV viraemia at week 24 of therapy, because they had minimal chance of achieving SVR with continued therapy.

Outcome	Group 1 (24 weeks' treatment)	Group 2 (48 weeks' treatment)	*p*-value
Viral response, *n* (%):			
4-week (RVR)	104 (68)	97 (63)	0.47
12-week (EVR)	142 (94)	148 (97)	0.17
End of treatment	136 (91)	142 (97)	0.06
End of follow-up (SVR)	87 (56)	117 (76)	< 0.001
Relapse rate	46 (34)	24 (17)	0.001

Percentages reported by paper (above) are incorrect if denominator is 154. For RVR, EVR, EOT, SVR and relapse rate, the percentages would be 67%, 92%, 88%, 56% and 29% for 24-week group, and 62%, 96%, 92%, 75% and 15% for 48-week group respectively.

	Group 1 (24 weeks' treatment)	Group 2 (48 weeks' treatment)	*p*-value
Predictability of SVR during treatment with RVR stratified by baseline viral load			
SVR by RVR, *n* (%):			
RVR	104 (76)	97 (98)	< 0.001
No RVR	49 (16)	56 (39)	0.01
< 400, 000 IU/ml	49 (94)	42 (100)	0.25
< 600, 000 IU/ml	61 (93)	50 (100)	0.13
< 800, 000 IU/ml	69 (94)	57 (100)	0.13
< 1,000,000 IU/ml	71 (92)	61 (100)	0.03
ALT normalisation, *n* (%)	75 (51)	107 (72)	< 0.001
Histological response, *n* (%)	71 (59)	97 (78)	0.001

	RVR			SVR			
	Univariate analysis (*p*-value)	Multivariate analysis		Univariate analysis (*p*-value)	Multivariate analysis		
		OR (95% CI)	*p*-value		OR (95% CI)	*p*-value	
HCV RNA level (< 800, 000 vs ≥ 800,000 IU/ml)	< 0.001	3.33 (1.96 to 5.64)	< 0.001	< 0.001	10.51 (5.47 to 20.21)	< 0.001	
	Group 1 (24 weeks)			**Group 2 (48 weeks)**			***p*-value**
Adverse events:							
Dose discontinuation for any adverse event *n* (%)	6 (4)			14 (9)			0.10
Dose reduction for:							
Any adverse event	69 (45)			82(53)			
Anaemia	60 (39)			68 (44)			
Neutropenia	34 (22)			42 (27)			
Serious adverse events, %:	3			7			0.11
Death, *n*	0			1			
All, *n*	4			11			
Treatment related, *n*	3			9			
Specific adverse events, *n* (%):							
Fever	35 (23)			33 (21)			
Rigour	19 (12)			13 (8)			
Fatigue	88 (57)			100 (65)			
Headache	28 (18)			35 (23)			
Myalgia	40 (26)			36 (23)			
Arthralgia	8 (5)			13 (8)			
Insomnia	61 (40)			69 (45)			
Irritability	19 (12)			22 (14)			
Depression	36 (23)			26 (17)			
Anorexia	63 (41)			80 (52)			
Constipation	10 (6)			15 (10)			
Diarrhoea	14 (9)			18 (12)			
Body weight loss[a]	19 (19)			46 (30)			0.03
Hair loss/alopecia	24 (16)			36 (23)			
Aphthous ulcer	22 (14)			34 (22)			
Cough	28 (18)			32 (21)			
Nasal congestion	13 (8)			17 (11)			
Tinnitus	13 (8)			20 (13)			
Dermatitis	44 (29)			48 (31)			
Injection reaction	22 (14)			29 (19)			
Anaemia	60 (39)			68 (44)			
Neutropenia	34 (22)			42 (27)			
Thrombocytopenia	25 (16)			23 (15)			

a Weight reduction of > 10% from the baseline weight.

Adverse events

In the 24-week group, severe adverse events included retinal ischaemia, hepatic decompensation, major depression and HCC (the first three events were considered to be treatment related). In the 48-week group, severe adverse events included hepatic decompensation in three patients and major depression, renal abscess, interstitial pneumonitis, diabetes mellitus, empyema, pulmonary tuberculosis, HCC, and acute pancreatitis in one patient each (the first nine events were considered to be treatment related)

Fifteen patients experienced serious adverse events during the study period; 12 (80%) were considered to be treatment related

Four patients developed hepatic decompensation, with ascites and hepatic encephalopathy, requiring cessation of PEG. Three of these had cirrhosis and one of them had advanced fibrosis

One death due to reactivation of pulmonary tuberculosis at week 36 of therapy was reported in the 48-week group

Methodological comments

Allocation to treatment groups: Eligible patients were assigned 1 : 1. Randomisation was performed with the use of block sizes of 4 or 6 by computer-generated assignment

Allocation concealment: NR

Blinding: Open-label trial. Biopsy pathologist was blind to clinical status of study participants. Not stated whether other outcome assessors were blinded

Analysis by ITT: Authors state analysis was by ITT for the primary efficacy end point. The secondary efficacy end points were analysed only for patients who had undergone paired biopsies or for patients with available baseline and follow up ALT levels. Treatment was prematurely discontinued in patients who were randomised to 48 weeks of treatment but continued to have HCV viraemia at week 24 of therapy, because they had minimal chance of achieving SVR with continued therapy. A total of 88% completed 48 weeks of therapy

Comparability of treatment groups at baseline: Groups appear comparable at baseline

Method of data analysis: The baseline characteristics of treatment groups were compared using the chi-squared test, Fisher's exact test, or Student's *t*-test. Treatment responses, including efficacy and safety, were compared using Fisher's exact test. A p-value < 0.05 was considered to be statistically significant, all statistical tests were two tailed

Sample size/power analysis: The sample size was estimated to be 152 patients in each group on the basis of a type I error rate of $\alpha = 0.05$ and a type 2 error rate of $\beta = 0.20$ for a primary two-sided test with the assumption of a 15% difference in SVR rates (60% and 75% for 24 and 48 weeks of treatment, respectively)

Attrition/dropout: Participants were considered withdrawn from the study if the investigator was concerned about treatment safety or if the patient missed four consecutive weeks of therapy. In Group 1, seven patients discontinued treatment, six due to adverse events or laboratory abnormalities, one declined treatment. In Group 2, four discontinued treatment due to adverse events or laboratory abnormalities. Fifteen patients in Group 2 discontinued after treatment completion: 10 were due to adverse events or laboratory abnormalities, two patients had a positive HCV RNA at week 24, one declined treatment and two were lost to follow-up

General comments

Generalisability: The study appears generalisable to Asian patients with genotype 1 only. Mean baseline viral load [$\log_{10}$ 5.7 = 501,000 IU/ml (Group 1) and $\log_{10}$ 5.8 = 630,957 IU/ml (Group 2)] was low and approximately 65% had RVR at week 4

Intercentre variability: NR

Conflict of interests: One author has been a consultant for Novartis and Roche, one author has been a consultant for Novartis and GSK. Another has been a consultant for Bristol–Myers Squibb (BMS), GSK, Novartis, Omrix, Roche and Schering-Plough and served on the speakers' bureau for Roche, BMS and GSK

Other: The percentages reported by the paper for RVR, EVR, EOT, SVR, relapse rate and SVR according to baseline viral load for both treatment groups are incorrect if the number of patients are calculated as a proportion of the whole group ($n = 154$). It is unclear what the denominator is

Quality criteria for assessment (updated CRD guidance)[a]

1.	Was the method used to generate random allocations adequate?	Yes
2.	Was the allocation adequately concealed?	Unclear
3.	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes
4.	Were outcome assessors blinded to the treatment allocation?	Unclear
5.	Was the care provider blinded?	No
6.	Was the patient blinded?	No
7.	Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No
8.	Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
9.	Did the analysis include an ITT analysis?	Yes
	If so, was this appropriate?	Yes
	If so, were appropriate methods used to account for missing data?	Unclear

a Answer: yes/no/unclear.

Yu and colleagues[54]

Reference and design	Intervention	Participants	Outcome measures
Author: Yu and colleagues[54,58] *Year*: 2008 (2007) abstract *Study design*: Open-label, multicentre RCT *No. of centres*: Four *Country*: Taiwan *Sponsor*: Taiwan Liver Research Foundation	**Group 1: 24 weeks** *n* = 100 *Drug 1*: PEG α-2a Dose: 180 µg/week s.c. Duration: 24 weeks *Drug 2*: RBV Dose: 1000 mg/day for body weight ≤ 75 kg and 1200 mg/day for body weight > 75 kg, oral, two divided doses Duration: 24 weeks **Group 2: 48 weeks** *n* = 100 *Drug 1*: PEG α-2a Dose: 180 µg/week s.c. Duration: 48 weeks *Drug 2:* RBV Dose: 1000 mg/day for body weight ≤ 75 kg and 1200 mg/day for body weight > 75 kg, oral, two divided doses Duration: 48 weeks	**Total numbers involved:** 200 Intervention 1: 100 Intervention 2: 100 **Treatment naive/non-responders/relapsers:** Treatment naive **Previous treatment:** NA **HCV/HIV co-infection:** No **Recruitment:** One medical centre and three regional hospitals in Taiwan from April 2005 to May 2007 **Inclusion criteria:** Previously untreated Taiwanese patients with HCV aged 18–65 years. Seropositive for HCV antibodies and HCV RNA, had undergone liver biopsy that was consistent with HCV within 1 year before entry, elevated serum ALT for ≥ 2 measurements within 6 months before trial entry, genotype 1 infection, neutrophil count > 1500 mm^{-3}, platelet count > 9×10^4 mm^{-3}, Hb level > 12 g/dl men and > 11 g/dl for women, serum creatinine level < 1.5 mg/dl, no pregnancy/lactation, and use of reliable method of contraception **Exclusion criteria:** HCV genotype infections other than HCV-1, hepatitis B surface antigen, HIV infection, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, Wilson disease, $alfa_1$-antitryspin deficiency, DC, overt hepatic failure, a current or history of alcohol abuse (≥ 20 g daily), psychiatric conditions, previous LT, or with evidence of HCC ***Baseline measurements*:** **Viral load (log IU/ml), mean (± SD):** Group 1: 5.43 ± 1.00 Group 2: 5.66 ± 0.95 *p* = 0.104 **Lower viral load, < 400,000 IU/ml, *n* (%):** Group 1: 55 (55%) Group 2: 56 (56%), *p* = not reported	**Primary outcomes:** SVR **Secondary outcomes:** RVR EVR EOT virological response Relapse rate Adverse events **Length of follow-up:** 24 weeks (following treatment end) **Methods of assessing outcomes:** Bi-weekly outpatient visits in the first month then monthly visits during remaining treatment period and follow-up At each visit patients underwent physical examination and adverse events were recorded HCV genotypes determined by Okamoto. Serum HCV RNA at baseline, weeks 4 and 12, end of treatment and 24 weeks after treatment determined by qualitative PCR. Serum HCV RNA at baseline measured by qualitative PCR (limit 615 IU/ml). Liver histology according to Knodell and Scheuer

Reference and design	Intervention	Participants	Outcome measures
		Serum ALT (IU/l) mean (± SD): Group 1: 156 ± 84 Group 2: 137 ± 92, *p*-value = 0.145 **Histology:** Fibrosis score, *n* (%): overall *p* = 0.306 F 0–2: Group 1: 75 (75), Group 2: 81 (81) F 3–4: Group 1: 25 (25), Group 2: 19 (19) **Necroinflammatory score, mean (± SD):** Group 1: 4.82 ± 2.55 Group 2: 4.41 ± 2.29 *p* = 0.241 **Genotypes, *n* (%):** 1 : 200 (100) 1a: 199 1b: 1 **Gender male, *n* (%):** Group 1: 57 (57%) Group 2: 58 (58%), *p*-value = 0.886 **Age (years), mean (± SD):** Group 1: 49.7 ± 11.6 Group 2: 49.1 ± 12, *p*-value = 0.729 **Ethnic groups, *n* (%):** NR **Mode of infection, *n* (%):** NR **Losses to follow-up:** Group 1: Treatment terminated early *n* = 3 (adverse events *n* = 3), lost to follow up *n* = 0 Group 2: Treatment terminated early *n* = 10 (Adverse events *n* = 8, laboratory abnormalities *n* = 1, insufficient response *n* = 1, lost to follow up *n* = 1) **Compliance:** NR	

PEG α, peginterferon alfa; RBV, ribavirin; s.c., subcutaneously.
EVR was defined as PCR-negative or at least a 2-$\log_{10}$ decline from baseline of serum HCV RNA at 12 weeks of treatment; EOT virological response was defined as PCR-negative serum HCV-RNA (< 50 IU/ml) at the end of treatment; 'relapse' was defined as HCV RNA re-appearance during the follow-up period in patients who achieved an EOT virological response. RVR was defined by PCR-negative serum HCV RNA (< 50 IU/ml) at 4 weeks of therapy; 'serum HCV RNA at baseline', weeks 4, 12 end of treatment and 24 weeks after therapy, were determined by qualitative PCR – levels at baseline and week 12 of treatment were measured using the branched DNA assay (Versant HCV RNA 3.0, Bayer, Tarrytown, NJ; quantification limit: 615 IU/ml); SVR was defined as HCV RNA PCR-seronegative by the end of treatment and throughout the follow-up period.

Outcome	Group 1, 24-week treatment (*n* = 100)	Group 2, 48-week treatment (*n* = 100)	*p*-value
Viral response, % (95% CI)			
4-week (RVR)	45 (35 to 55)	42 (32 to 52)	
EVR	95.9 (92 to 100)	93 (88 to 98)	
End of treatment	93 (88 to 98)	90 (84 to 96)	
Relapse	36.6 (27 to 47)	12.2 (5 to 19)	< 0.0001
End of follow-up (SVR)	59 (49 to 69)	79 (71 to 87)	0.002
SVR by RVR			
RVR, % (*n*/*N*, 95% CI)	88.9 (40/45, 0.8 to 0.98)	100 (42/42)	0.056[a]
No RVR, % (*n*/*N*, 95% CI)	34.5 (19/55, 0.22 to 0.47)	63.8 (37/58, 0.51 to 0.76)	0.002[b]

a Difference 11.1%, (95% CI –22.6% to 4.2%).
b Difference 29.2% (95% CI –48% to –13.4%).

	Group 1: 24 weeks	Group 2: 48 weeks	*p*-value
SVR by viral load and RVR, % (n/N, 95% CI):			
RVR and LVL (*n* = 52)	96.4% (27/28, 89 to 103)	100% (24/24)	Difference –3.6% (–14.3% to –0.6%), *p* = 1.000
RVR and HVL (*n* = 35)	76.5 (13/17, 56 to 97)	100 (18/18)	0.045
Relapse rate, % (*n*/*N*, 95% CI)	36.6 (34/93, 27 to 47)	12.2 (11/90, 5 to 19)	< 0.0001
Relapse rate by RVR:			
RVR	11.1 (5/45, 0.02 to 0.2)	0 (0/42)	Difference 11.1 (–0.4 to 18)
No RVR	60.4 (29/48, 0.46 to 0.74)	22.9 (11/48, 0.11 to 0.35)	Difference 37.5 (17.2 to 53.7)
Relapse rate by viral load and RVR, % (*n*/*N*, 95% CI):			
RVR and LVL (*n* = 52)	3.6 (1/28, –3 to 11)	0 (0/24)	Difference 3.6 (–7.2 to 6.6), *p* = 1.000
RVR and HVL (*n* = 35)	23.5 (4/17, 3 to 44)	0 (0/18)	0.045
Adverse events n *(%):*			
Serious adverse events	1 (1)	1 (1)	
Discontinuation	3 (3)	10[c] (10)	0.045
Dose modification or transient interruption for adverse events or laboratory abnormalities:			
PEG α-2a	22 (22)	24 (24)	0.737
RBV	49 (49)	60 (60)	0.118
PEG α-2a or RBV	54 (54)	65 (65)	0.113
Influenza-like symptoms including fever, chills, headache	76 (76)	74 (74)	0.744
Gastrointestinal symptoms:			
Anorexia or nausea	50 (50)	53 (53)	0.671
Diarrhoea	18 (18)	26 (26)	0.172
Psychiatric symptoms:			
Anxiety	31 (32)	36 (36)	0.454
Depression	24 (24)	34 (34)	0.119
Insomnia	59 (59)	65 (65)	0.382
Dermatological symptoms			
Hair loss	66 (66)	72 (72)	0.359
Skin rash	54 (55)	66 (66)	0.083
Haematological abnormality:			
Leucopenia (white cell count < 1500/mm^3)	5 (5)	8 (8)	0.39
Anaemia (Hb < 10 g/dl)	39 (39)	48 (48)	0.199
Thrombocytopenia (< 50/mm^3)	2 (2)	6(6)	0.279
Abnormal thyroid tests	13 (13)	15 (15)	0.684

c Eight of these were owing to adverse events, one to insufficient serum creatinine level and one because of insufficient response.
Serious adverse event: one patient with cirrhosis experienced variceal bleeding at EOT, one patient experienced severe myalgias over the lower back, resulting in disability of gait during treatment.

	Group 1: 24 weeks		Group 2: 48 weeks	
	SVR(–)	SVR(+)	SVR(–)	SVR(+)
Additional results/comments				
Baseline HCV RNA level, log IU/ml	5.92 ± 0.60	5.09 ± 1.08[d]	5.93 ± 0.86	5.58 ± 0.96[e]
< 400,000 IU/ml, *n* (%)	11 (26)	34 (57.6)[f]	8 (38.1)	36 (45.6)[g]
≥ 400,000 IU/ml, *n* (%)	30 (73.2)	25 (42.4)[h]	13 (61.9)	43 (54.4)[h]

d $p < 0.0001$ between those with and without SVR in 24-week group (Group 1).
e $p = 0.132$ between those with and without SVR in 48-week group (Group 2).
f $p = 0.002$ between those with and without SVR in 24-week group (Group 1).
g $p = 0.540$ between those with and without SVR in 48-week group (Group 2).
h *p*-value not reported.

Adverse events were graded as mild, moderate, severe or potentially life threatening

Significantly more patients with a lower baseline viral load (< 400, 000 IU/ml) achieved an RVR [RVR(+) 59.8% vs RVR(–) 32.7% $p < 0.0001$]

Lower baseline viral load (< 400,000 IU/ml) was the only significant factor associated with RVR with an odds ratio of 3.052 (95% CI 1.706 to 5.458)

The influence of other factors associated with the RVR (baseline demographical characteristics, ALT, liver histopathology, fibrosis and mean dose of RBV) were reported in the publication but none was significant and are not presented here

In the 24-week group, RVR ($p < 0.0001$), lower viraemia (< 400,000 IU/ml) ($p = 0.002$), younger age ($p = 0.055$) and 80/80/80 adherence ($p = 0.056$) were predictive factors associated with a higher SVR rate (reviewer note: last two factors are borderline significance). Other factors predictive of SVR (baseline demographical characteristics, ALT, liver histopathology and fibrosis) were reported in the publication but these were not significant and are not reported here

Independent predictors of SVR in the 24-week group were RVR and lower viraemia with odds ratios (CI) of 10.84 (3.189 to 36.82) and 3.087 (1.031 to 9.239), respectively. In the 48-week group, RVR was the only independent predictor of SVR, with an odds ratio of 'infinity'

Independent predictors for SVR for all 200 patients (by logistic regression analysis) were RVR, followed by treatment duration, RBV dose and baseline viral load

For 148 patients with either high viraemia or without an RVR the relapse rate was significantly higher in the 24-week group (50.8%, 95% CI 39 to 63) than in the 48-week group (16.7%, 95% CI 8 to 26) $p < 0.0001$). The SVR rate was significantly lower in the 24-week group (44.4%, 95% CI 33 to 56) than in the 48-week group (71.4%, 95% CI 62 to 82, $p = 0.001$)

Methodological comments

Allocation to treatment groups: Randomly by computer coding, 1 : 1 randomisation ratio. The randomisation sequence was centrally accessed through telephone or direct office visit

Allocation concealment: The details of the series were contained in a set of sealed envelopes and unknown to the investigators who enrolled subjects

Blinding: Open label, therefore no blinding of participants or care providers. Liver histology graded and staged by single pathologist blinded to treatment, no further details of blinding of outcome assessors

Analysis by ITT: ITT All patients receiving one dose of either study drug were analysed

Comparability of treatment groups at baseline: Groups were comparable at baseline, there were no statistically significant differences (*p*-values were reported)

Method of data analysis: Frequency was compared between groups using the chi-squared test with the Yates correction, or Fisher's exact test. Groups means, presented as mean ± SD, were compared using analysis of variance and Student *t*-test, or Mann–Whitney test when appropriate. Serum HCV RNA levels were expressed after logarithmic transformation of original values. Analysis on SPSS. All statistical analyses were based on two-sided hypothesis test with a significance level of $p < 0.05$

Sample size/power analysis: The study was designed to detect a difference of 12% with 80% power or more, anticipating a 10% dropout rate.
Attrition/dropout: 199/200 patients completed the study. One patient in the 48-week group was lost to follow-up 2 months after cessation of treatment and was classified as a non-responder for final analysis

General comments

Generalisability: The study appears generalisable to treatment-naive, Asian patients with genotype 1 HCV. Mean baseline viral load (log 5.43 = 269,153 IU/ml and log 5.66 = 457,088 IU/ml for 24 weeks and 48 weeks, respectively) was low and approximately 55% had LVL (< 400,000 IU/ml). Approximately 43% had RVR at week 4

Inter-centre variability: NR

Conflict of interests: It is stated that the sponsor did not participate in the study design, patient collection, analysis or interpretation

Quality criteria for assessment (updated CRD guidance)[a]

1.	Was the method used to generate random allocations adequate?	Yes
2.	Was the allocation adequately concealed?	Yes
3.	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes
4.	Were outcome assessors blinded to the treatment allocation?	Unclear
5.	Was the care provider blinded?	No
6.	Was the patient blinded?	No
7.	Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No
8.	Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
9.	Did the analysis include an ITT analysis?	Yes
	If so, was this appropriate?	Yes
	If so, were appropriate methods used to account for missing data?	Yes

a Answer: yes/no/unclear.

Yu and colleagues[55]

Reference and design	Intervention	Participants	Outcome measures
Author: Yu and colleagues[55] Year: 2007 *Study design*: Open-label, multicentre RCT *No. of centres*: 4 *Country*: Taiwan *Sponsor*: Taiwan Liver Research Foundation	**Intervention 1:** 24 weeks *n* = 100 *Drug 1*: PEG α-2a Dose: 180 µg once/week, s.c. Duration: 24 weeks *Drug 2*: RBV Dose: 1000 mg/day for patients ≤ 75 kg, 1200 mg/day for patients > 75 kg (oral, two divided doses) Duration: 24 weeks **Intervention 2:** 16 weeks *n* = 50 *Drug 1*: PEG α-2a Dose: 180 µg once/week, s.c. Duration: 16 weeks *Drug 2*: RBV Dose: 1000 mg/day for patients ≤ 75 kg, 1200 mg/day for patients > 75 kg (oral, two divided doses) *Duration*: 16 weeks	**Total numbers involved:** 326 screened, 150 eligible and randomised. *n* = 100 Group 1, *n* = 50 Group 2 **Treatment naive/non-responders/relapsers:** Treatment naive **Previous treatment:** NA **HCV/HIV co-infection:** No **Recruitment:** A medical centre and three regional core hospitals in Taiwan between September 2003 and December 2005 **Inclusion criteria:** Previously untreated adults (18–65 years) with HCV genotype 2, seropositive for HCV antibodies and for HCV RNA PCR, undergone liver biopsy within 1 year before entry (with result of chronic hepatitis C), increased serum ALT defined as ≥ 1.5 times the ULN for two or more measurements within 6 months preceding trial entry, neutrophil count > 1500/mm^3, platelet count > 9 × 10^4/mm^3, Hb > 12 g/dl for men and 11 g/dl for women, serum creatinine < 1.5 mg/dl, no pregnancy or lactation and using reliable contraception for women **Exclusion criteria:** HCV genotype other than type 2, hepatitis B surface antigen, HIV infection, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, Wilson's disease α-antitrypsin deficiency, DC (Child–Pugh class B or C), overt hepatic failure, current or history of alcohol misuse (≥ 20 g/day) psychiatric condition, previous liver transplant, evidence of HCC ***Baseline measurements*:** **Viral load (log IU/ml), mean (± SD):** 4.88 (1.07) Group 1, 4.98 (1.08) Group 2, *p* = 0.62 **Serum ALT (IU/l), mean (± SD):** 108.9 (68.75) Group 1, 107 (64.6) Group 2, *p* = 0.857 **Histology:** *Fibrosis, n (%)*: *p* = 0.832 F 0–2: 80 (80) Group 1, 39 (78) Group 2 F 3–4: 20 (20) Group 1, 11 (22) Group 2 *Necroinflammatory score, mean (± SD)*: 4.84 (2.34) Group 1, 5.48 (3.32) Group 2, *p* = 0.226 *Steatosis, n (%)*: *p* = 1 None (0): 67 (67) Group 1, 34 (68) Group 2 Mild (1): 28 (28) Group 1, 13 (26) Group 2 Moderate – severe (2–3): 5 (5) Group 1, 3 (6) Group 2 ***Genotypes, n (%)*:** 100% genotype 2 **Gender male, *n* (%):** 58 (58%) Group 1, 32 (64%) Group 2 **Age (years), mean (± SD):** 49.9 (10.69) Group 1, 50.8 (9.74) Group 2, *p* = 0.621 ***Ethnic groups, n (%)*:** 100% Asian (Taiwanese) ***Mode of infection, n (%)*:** NR ***Losses to follow-up*:** 0 **Compliance:** *80/80/80 adherence, n (%)*: 73 (73) Group 1, 43 (86) Group 2	**Primary outcomes:** SVR **Secondary outcomes:** RVR ETVR (EOT virological response) Relapse rate Adverse events **Length of follow-up:** 24 weeks after cessation of treatment **Methods of assessing outcomes:** Patients had bi-monthly out-patient visits during the first month and monthly visits thereafter where they underwent a physical examination and adverse events were recorded. A citation was given (ref. 18) for the method by which HCV genotypes 1a, 1b, 2a, 2b and 3a were determined. Serum HCV RNA levels at baseline and during treatment week 4 were measured using the branched DNA assay, quantification limit 615 IU/ml. Serum HCV RNA at baseline, during treatment weeks 4, 12, EOT and at follow-up was determined by standardised automated qualitative PCR, detection limit 50 IU/ml. Scheuer and Knodell scoring system used for liver histology

ALT, alanine transaminase level; ETVR, EOT virological response (defined as PCR-negative serum HCV RNA at end of treatment); HCC, hepatocellular carcinoma; PCR, polymerase chain reaction assay; 80/80/80 adherence, patients who had received > 80% of expected PegIFN and RBV doses and completed at least 80% of expected duration; PEG α, peginterferon alfa; RBV, ribavirin; RVR, defined as PCR-negative serum HCV RNA at 4 weeks of treatment); s.c., subcutaneously; SVR, defined as PCR-negative serum HCV RNA by end of treatment and end of follow-up); 'non-response' defined as not achieving SVR; 'relapse' defined as re-appearance of HCV RNA during follow-up period in patients who achieved an ETVR; ULN, upper limit of normal.

Outcome	Intervention 1 (24 weeks)	Intervention 2 (16 weeks)	*p*-value
Viral response, % (*n*/*N*, 95% CI):			
4-week (RVR)	87 (87/100, 80 to 94)	86 (43/50, 76 to 96)	
12-week (EVR)	–	–	
End of treatment (ETVR)	98 (98/100, 95 to 100)	100	
End of follow-up (SVR)	95% (95/100, 91 to 99)	94 (47/50, 87 to 100)	Difference –1%, 95% CI 9 to 7
SVR by RVR, % (*n*/*N*):			
RVR	98 (85/87)	100 (43/43)	1
No RVR	77 (10/13)	57 (4/7)	0.610
SVR by baseline HCV RNA, % (*n*/*N*):			
< 800,000 IU/ml	95 (81/85)	95 (39/41)	1
> 800,000 IU/ml	93 (14/15)	89 (8/9)	1
SVR by viral load & RVR, % (*n*/*N*)	NR	NR	
Other viral response outcomes:			
Relapse rate, % (*n*/*N*, 95% CI)	3.1 (3/98, –1 to 13)	6 (3/50, 0 to 7)	Difference (not reported) 95% CI –10.4 to 4.5
Relapse rate by baseline HCV RNA, % (*n*/*N*):			
< 800,000 IU/ml	3.6 (3/84)	4.9 (2/41)	1.000
> 800,000 IU/ml	0 (0/14)	11.1 (1/9)	0.391
Relapse rate by RVR,% (*n*/*N*):			
RVR	2.3 (2/87)	0 (0/43)	0.554
No RVR	9.1 (1/11)	42.9 (3/7)	0.245
Biochemical response, % (*n*/*N*):	NR	NR	1
End of treatment			
End of follow-up			
Histology (proportion with improvement):	NR	NR	1
Inflammation, mean change			
Fibrosis, mean change			
Adverse events, n (%)			
Dose discontinuation for any adverse event	1 (1%)	0	1
Dose modification for adverse events or lab abnormalities:			
PEG	9 (9)	4 (8)	1
RBV	51 (51)	23 (46)	0.564
PEG or RBV	54 (54)	26 (52)	0.817
Specific adverse events			
Flu-like symptoms:			
Fever	55 (55)	29 (58)	0.727
Chills	28 (28)	12 (24)	0.602
Headache	39 (39)	21 (42)	0.724
Gastrointestinal symptoms:			
Anorexia	46 (46)	20 (40)	0.601
Nausea	15 (15)	3 (6)	0.181
Diarrhoea	9 (9)	5 (10)	1

Outcome	Intervention 1 (24 weeks)	Intervention 2 (16 weeks)	*p*-value
Psychiatric symptoms:			
Anxiety	7 (7)	4 (8)	1
Depression	10 (10)	3 (6)	0.545
Insomnia	57 (57)	23 (46)	0.227
Dermatological symptoms:			
Hair loss	49 (49)	10 (20)	0.001
Skin rash	54 (54)	22 (44)	0.248
Haematological abnormality:			
Leucopenia (white cell count $<1500/mm^3$)	2 (2)	1 (2)	1
Anaemia (Hb <10 g/dl)	53 (53)	27 (54)	1
Thrombocytopenia ($<50{,}000/mm^3$)	1 (1)	0	1
Abnormal thyroid function tests	13 (13)	4 (8)	0.362

Additional results/comments (e.g. early response factors, QoL)

Virological response

Within treatment groups, mean (±SD) baseline HCV RNA level was not significantly different in patients who achieved an SVR compared to those who did not for both the 24-week Group (4.86 ± 1.08 vs 5.33 ± 0.55, $p=0.342$) and the 16-week Group (4.93 ± 1.1 vs 5.63 ± 0.35, $p=0.283$)

Within treatment groups, significantly more patients who achieved an SVR had an RVR at 4 weeks compared with those who did not achieve an SVR in both the 24-week Group [90% (85/95) vs 40% (2/5), $p=0.015$] and the 16-week Group [92% (43/47) vs 0% (0/3), $p=0.002$]. No other baseline factors were significantly associated with an SVR

Factors significantly associated with SVR were RVR at week 4 (OR 40.76, 95% CI 5.964 to 278.6) and patient's age (OR 0.834, 95% CI 0.721 to 0.965). Treatment duration was not associated with SVR (OR 1.241, 95% CI 0.186 to 8.279)

For patients without an RVR, the relapse rate was higher in the 16-week Group (42.9%, 95% CI –7% to 92%) than in the 24-week Group (9.1%, 95% CI –11% to 29%), and the SVR rate was lower in the 16-week Group (57%, 95% CI 20 to 94) than in the 24-week Group (77%, 95% CI 54 to 99), but neither were statistically significant

The influence of a number of other prognostic factors (baseline demographical characteristics, liver histopathology, 80/80/80 adherence and received doses of PEG and RBV) on the SVR rate were reported in the publication, but none was significant and they are not presented here. Similarly, between group differences in relapse rate and SVR rate were reported by age, sex, body mass index, fibrosis, steatosis, 80/80/80 adherence, received RBV doses and dose modifications, but none was significant

Results were reported for mean RBV dose throughout the treatment period stratified by RVR, SVR and treatment duration (but these are not presented here)

Safety

Treatment was discontinued by 1 patient (24-week Group) due to anaemia and leucopenia at week 23

PEG dose reductions were due to adverse events ($n=5$), leucopenia ($n=3$), anaemia ($n=4$) and thrombocytopenia ($n=1$)

Adverse events were typical of those previously reported for PEG and RBV combination treatment

No serious adverse event was reported

Methodological comments

Allocation to treatment groups: Patients were assigned randomly by computer coding in a 1 : 2 randomisation ratio

Allocation concealment: The computer-generated code was generated by a contract research organisation independent of the study and was centrally accessed through telephone or direct office visit. Details of the series were contained in sealed envelopes and were unknown to any of the investigators who enrolled patients for the study

Blinding: No blinding of participants and care providers (open label) and blinding of outcome assessors not reported, except for biopsy pathologists

Analysis by ITT: States that evaluation of efficacy was based on ITT analysis and that all patients receiving a treatment dose of PEG or RBV were analysed. SVR was reported for all 150 randomised patients

Comparability of treatment groups at baseline: Participant baseline demographics were well matched between arms with no statistically significant differences (*p*-values reported). Patients in 16-week Group had slightly higher 80/80/80 adherence than the 24-week Group (86% vs 73%, $p = 0.073$), but the difference was not significant

Method of data analysis: Frequency was compared between groups using the chi-squared test, with the Yates correction, or Fisher's exact test. Group means were compared using analysis of variance and Student's *t*-test or non-parametric Mann–Whitney *U*-test when appropriate. Serum HCV RNA levels were expressed after log transformation of original values. Stepwise logistical regression was used to analyse which variables had a better predictive value for SVR (using SPSS version12.0). All statistical analyses were based on two-sided hypothesis tests with a significance level of $p < 0.05$

Sample size/power analysis: Assuming an SVR rate of 82% for 24 weeks' treatment and no SVR if untreated, the study was powered to detect a difference of ≥24.6% with 80% power, anticipating a 10% dropout rate. It is reported that this margin is equivalent to other published data (reference cited)

Attrition/dropout: Reasons for the one dropout were provided

General comments

Generalisability: Treatment-naive, Taiwanese Asian patients with genotype 2 HCV. Mean baseline viral load (log 4.88 = 75,860 IU/ml and log 4.98 = 95,500 IU/ml for 24 weeks and 16 weeks, respectively) was low, and when SVR was measured (at 24-week follow-up) approximately 83% had baseline LVL (< 800,000 IU/ml). The majority (86%) had RVR at week 4

Inter-centre variability: NR

Conflict of interests: None

Quality criteria for assessment (updated CRD guidance)[a]

1.	Was the method used to generate random allocations adequate?	Yes
2.	Was the allocation adequately concealed?	Yes
3.	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes
4.	Were outcome assessors blinded to the treatment allocation?	Unclear
5.	Was the care provider blinded?	No
6.	Was the patient blinded?	No
7.	Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No
8.	Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
9.	Did the analysis include an ITT analysis?	Yes
	If so, was this appropriate?	Yes
	If so, were appropriate methods used to account for missing data?	Yes

a Answer: yes/no/unclear.

von Wagner and colleagues[56]

Reference and design	Intervention	Participants	Outcome measures
Author: von Wagner and colleagues[56] *Year*: 2005 *Study design*: Multicentre, Phase IIIb RCT *No. of centres*: 6 *Country*: Germany *Sponsor*: Hoffmann-La Roche and the German Hepatitis Network of Competence (Hep-Net)	*n* = 153 **PEG -2a** Dose: 180 µg/week, s.c. Duration: 8 weeks **RBV** Dose: 800 mg/day for patients ≤ 65kg, 1000 mg/day for patients 65–85 kg, 1200 mg/day for patients > 85 kg, oral Duration: 8 weeks Those with RVR at week 4 randomised at week 8 to: **Intervention 1**: 16 weeks, RVR (Group A) *n* = 71 *Drug 1*: *PEG α-2a* Dose: 180 µg/week, s.c. Duration: 8 weeks *Drug 2*: *RBV* Dose: 800 mg/day for patients ≤ 65 kg, 1000 mg/day for patients 65–85 kg, 1200 mg/day for patients > 85 kg; oral Duration: 8 weeks (total duration 16 weeks) **Intervention 2**: **24 weeks, RVR (Group B)** *n* = 71 *Drug 1*: *PEG α-2a* Dose: 180 µg/week, s.c. Duration: 16 weeks *Drug 2*: *RBV* Dose: 800 mg/day for patients ≤ 65kg, 1000 mg/day for patients 65–85 kg, 1200 mg/day for patients > 85 kg; oral Duration: 16 weeks (total duration 24 weeks) Patients without an RVR at week 4 allocated at week 8 to: *Intervention 3: 24 weeks, no RVR (Group C)*[a] *n* = 11 *Drug 1*: *PEG α-2a* Dose: 180 µg/week, s.c. Duration: 16 weeks	**Total numbers involved:** 153 enrolled; 142 randomised at week 8 (Groups A and B) **Treatment naive/non-responders/relapsers:** Treatment naive **Previous treatment:** NA **HCV/HIV co-infection:** No **Recruitment:** Six tertiary referral centres in Germany between January 2002 and March 2004 **Inclusion criteria:** Adults (> 18 years), not previously treated with IFN and/or RBV, with compensated chronic HCV genotype 2 or 3, positive for anti-HCV antibody and HCV RNA > 600 IU/ml, liver biopsy within 18 months prior to screening, ≥ 1 serum ALT level elevated at screening or study entry, neutrophil count ≥ 1500/l, platelet count ≥ 90,000/l, Hb ≥ 13g/dl for men and ≥ 12g/dl for women **Exclusion criteria:** Any other cause of liver disease or other relevant disorders including HIV or hepatitis B co-infection, clinically significant haematological, hepatic, metabolic, renal, rheumatological, neurological or psychiatric disease, clinically significant cardiac or cardiovascular abnormalities, organ grafts, systemic infection, clinically significant bleeding disorders, evidence of malignant neoplastic disease, concomitant immunosuppressive medication, excessive daily intake of alcohol or drug abuse within past year, pregnancy, lactation, male partners of pregnant women ***Baseline measurements*:** **Viral load (log IU/ml), mean (± SD):** 5.8 (±0.7) Group A 5.8 (±0.8) Group B 5.7 (±0.5) Group C **Serum ALT × ULN (IU/l), mean (± SD):** 2.8 (± 2.9) Group A 2.8 (± 2.0) Group B 2.4 (± 0.9) Group C **Histology:** *Classification system used: Ishak* *Fibrosis score, mean (± SD)*: 1.6 (±1.4) Group A 1.6 (±1.1) Group B 2.4 (±2.3) Group C *Necroinflammatory score (total inflammation), mean (± SD)*: 4.3 (±2.4) Group A 4.6 (±2.4) Group B 5.0 (±4.0) Group C	**Primary outcomes:** SVR **Secondary outcomes:** RVR EOT virological response Sustained biochemical response Virological response according to genotype and baseline viraemia Adverse events **Length of follow-up:** 24 weeks after end of treatment **Methods of assessing outcomes:** Evaluated at weeks 2, 4, 8, 12, 16, 20 and 24 (Groups B and C) during treatment and at weeks 4, 12 and 24 following end of treatment. During treatment, HCV RNA quantified by PCR assay, end of treatment and SVR assessed by qualitative PCR assay (lower detection limit 50 IU/ml). HCV genotyping performed by reverse hybridisation; histology classified according to Ishak

Reference and design	Intervention	Participants	Outcome measures
	Drug 2: *RBV* Dose: 800 mg/day for patients ≤65kg, 1000 mg/day for patients 65–85 kg, 1200 mg/day for patients >85 kg; oral Duration: 16 weeks (total duration 24 weeks)	**Genotypes, *n* (%):** Genotype 2, genotype 3: 19/71 (27%) Group A,[a] 51/71 (72%) Group A 19/71 (27%) Group B, 52/71 (73%) Group B 1/11 (9%) Group C, 10/11 (91%) Group C ([a]G2 or 3 could not be differentiated in one patient) **Gender male, *n* (%):** 52 (73%) Group A 41 (58%) Group B 4 (36%) Group C **Age (years), mean (± SD):** 38 (± 9) Group A 39 (± 11) Group B 42 (± 10) Group C **Ethnic groups, *n* (%):** NR **Mode of infection, *n* (%):** NR **Losses to follow-up:** 144/153 (94%) completed treatment; *n* = 9 (3 Group A, 6 Group B) lost to follow-up. However, those who withdrew prematurely from treatment were encouraged to return for follow-up. 142/153 (93%) completed follow-up (68 Group A, 65 Group B and 9 Group C) **Compliance:** *n* = 9 discontinued treatment (1 Group A, 6 Group B, 2 Group C), *n* = 8 prematurely withdrew for non-safety reasons (1 Group A, 5 Group B, 2 Group C)	

ALT, alanine transaminase level; PCR, polymerase chain reaction assay; PEG α, peginterferon alfa; RBV, ribavirin; RVR, defined as serum HCV RNA < 600 IU/ml at 4 weeks of treatment; SVR, defined as undetectable serum HCV RNA 24 weeks after end of treatment; s.c., subcutaneously; ULN, upper limit of normal.
a Not randomised.

Outcome	Group A (*n* = 71), 16 weeks, RVR	Group B (*n* = 71), 24 weeks, RVR	Group C (*n* = 11), 24 weeks, no RVR
Viral response, % (*n*/*N*):			
4-week (RVR)	100	100	0
12-week (EVR)	–	–	–
End of treatment	94 (67/71)	85 (60/71)	72[c]
End of follow-up (SVR)	82 (58/71)[b]	80 (57/71)	36[d]
SVR by genotype and baseline viral load, % (*n*/*N*):			
Genotype HCV-2 (*n* = 38):			
≤800,000 IU/ml	100 (6/6)	100 (6/6)	–
>800,000 IU/ml	93 (12/13)	93 (12/13)	–
Genotype HCV-3 (*n* = 103):			
≤800,000 IU/ml	93 (27/29)	84 (21/25)	–
>800,000 IU/ml	54 (12/22)	67 (18/27)[e]	–
SVR by baseline viral load and RVR, % (*n*/*N*):			
≤800,000 IU/ml (*n* = 66)	94 (33/35)	87 (27/31)	–
>800,000 IU/ml (*n* = 75)	69 (24/35)	75 (30/40)	–

b Difference of at most 11.5% (97.5% one-sided CI) for Group A vs B.
c *p* = NS for Group B vs C.
d *p* = 0.005 for Group B vs C.
e *p* > 0.2 for Group A vs B.

Outcome	Group A ($n=71$), 16 weeks, RVR	Group B ($n=71$), 24 weeks, RVR	Group C ($n=11$), 24 weeks, no RVR
Biochemical response, % (n/N):			
End of treatment	–	–	–
End of follow–up	89	87	67
Histology:			
Inflammation	NR	NR	NR
Fibrosis	NR	NR	NR
Discontinuation:			
For adverse events	0	1 (1.4%)[f]	0
For other reason	1 (1.4%)	5 (7.0%)	2 (18.2%)
Dose modification for adverse events/laboratory abnormalities:			
PEG	5 (7.0%)	13 (18.8%)	4 (36.4%)
RBV	6 (8.5%)	8 (11.3%)	3 (27.3%)
Specific adverse events:[g]			
Flu-like symptoms	37 (52.1%)	33 (46.5%)	2 (18.2%)
Fatigue	26 (36.6%)	30 (42.3%)	8 (72.7%)
Pruritus	19 (26.8%)	24 (33.8%)	3 (27.3%)
Headache	18 (25.4%)	22 (31.0%)	6 (54.5%)
Anorexia	16 (22.5%)	19 (26.8%)	3 (27.3%)
Alopecia	15 (21.1%)	18 (25.4%)	2 (18.2%)
Asthenia	12 (16.9%)	18 (25.4%)	2 (18.2%)
Pain	9 (12.7%)	16 (22.5%)	5 (45.5%)
Dyspnoea	10 (14.1%)	16 (22.5%)	3 (27.3%)
Sleeping disturbance	9 (12.7%)	16 (22.5%)	4 (36.4%)
Pyrexia	10 (14.1%)	13 (18.3%)	3 (27.3%)
Dry skin	13 (18.3%)	9 (12.7%)	0
Aggressivity	8 (11.3%)	12 (16.9%)	0
Depression	8 (11.3%)	10 (14.1%)	2 (18.2%)
Chills	10 (14.1%)	8 (11.3%)	1 (9.1%)
Nausea	5 (7.0%)	11 (15.5%)	3 (27.3%)
Dry mouth	4 (5.6%)	8 (11.3%)	4 (36.4%)

f Intravenous drug abuse.
g Related to treatment, as judged by investigators, that occurred in at least 10% of patients who received at least one dose of study medication.

Additional results/comments (e.g. early response factors, QoL)

Virological response

After first 4 weeks of treatment, RVR (HCV RNA < 600 IU/ml) was achieved by 142/152 (93%) patients, made up of 37/38 (97%) genotype 2 and 103/112 (92%) genotype 3 ($p > 0.2$). These patients and one patient who was negative at week 2 with a missing HCV RNA result at week 4 were randomised to groups A ($n = 71$) and B ($n = 71$)

An overall ITT EOT response was achieved in 135/153 patients (88%), and an SVR in 119/153 patients (78%)

SVR according to genotype and pre-treatment viraemia

SVR in genotype HCV-2 patients were higher than in HCV-3 patients (92% vs 73%, respectively) (no *p*-value reported), and were not affected by pretreatment viraemia. However, HCV-3 patients with a baseline viraemia > 800,000 IU/ml achieved a significantly lower SVR than patients with baseline viraemia ≤ 800,000 IU/ml (59% vs 85%, respectively, $p = 0.003$)

There were no significant differences between groups A and B for SVR rates for patients with either HCV-2 or HCV-3

Predictors of SVR

From multivariate logistic regression analysis of all patients, genotype HCV-2, LVL and low γ-glutamyltransferase (GGT) value were independent factors of SVR. Based on patients with HCV-3 only, baseline viral load ($p = 0.01$) and GGT value ($p = 0.02$) remained as independent negative predictors for SVR. Fibrosis score and GGT were slightly higher in patients without a RVR (Group C) compared with patients with RVR (Groups A and B); however, differences did not reach statistical significance

Biochemical response

Sustained biochemical response was observed in 110/115 sustained virological responders (96%), whereas five sustained virological responders did not show a biochemical response with ALT levels ranging up to 2.95 times the upper limit of normal. Each of the five subjects was infected with genotype HCV-2

Adverse events

Seven serious adverse events were reported (bacterial infection, carcinoma, diverticulitis, paranoid reaction, pneumonia, pregnancy of partner, tuberculosis)

Adverse events were similar to those previously reported for PEG + RBV. In general, the frequency of adverse events was lower in Group A than in Groups B and C. (Reviewer note: No statistical comparison reported.) Neutropenia (3%) and anaemia (6%) were the most common adverse events leading to dose modification

Methodological comments

Allocation to treatment groups: No details about the randomisation method were reported. Patients with a RVR at week 4 of therapy were randomised 1 : 1 at week 8. Patients were stratified according to baseline viraemia (≤ 800,000 IU/ml vs > 800,000 IU/ml) and treatment centre.

Allocation concealment: NR

Blinding: Patients randomised at week 8 were informed about their treatment group assignment at the next clinical visit and were therefore not blinded. No details reported regarding blinding of outcome assessors

Analysis by ITT: ITT analysis for efficacy and safety variables ($n = 153$). One patient with a negative HCV RNA result at week 2 and missing data at week 4 was allocated to the RVR group (not reported whether Group A or B). One patient with missing data at weeks 2 and 4 was allocated to Group C

Comparability of treatment groups at baseline: Generally baseline demographic and disease characteristics were comparable across treatment groups. However, mean fibrosis score was higher in Group C vs Groups A and B (2.4 vs 1.6 and 1.6, respectively); also the proportion of genotype 3 patients was higher in Group C vs Groups A and B (91% vs 72% and 73%, respectively). Characteristics for Group A vs B were comparable. No statistical comparison was presented

Method of data analysis: The primary statistical analysis was the determination of a one-sided 97.5% CI for the difference in SVR rates between treatment groups A and B. Fisher's exact test and chi-squared tests were applied to compare different rates. Multivariate logistic regression was performed to identify independent predictors of RVR and SVR. Unless stated otherwise, *p*-values of < 0.05 were considered significant

Sample size/power analysis: The study was powered to detect a difference of 25% or more with a power of at least 80%

Attrition/dropout: Numbers reported but reasons not fully reported

Other: SVR rates reported for Group B in text are not consistent. Top right paragraph on p. 524 reports an SVR of 81% and EOT response of 84% for Group B, but in the previous paragraph reported 80% and 85%, respectively. Differences are possibly due to rounding of figures

General comments

Generalisability: Treatment-naive patients with genotype 2 and 3 HCV. Mean baseline viral load ($\log_{10}$ 5.8 = 631,000 IU/ml, $\log_{10}$ 5.8 = 631,000 and $\log_{10}$ 5.7 = 501,200 IU/ml for Group A, Group B and Group C, respectively) was low and all patients in Groups A and B had RVR at week 4

Intercentre variability: NR

Conflict of interests: The study was partly supported by the drug manufacturer (Roche)

Quality criteria for assessment (updated CRD guidance)[a]

1.	Was the method used to generate random allocations adequate?	Unclear
2.	Was the allocation adequately concealed?	Unclear
3.	Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Yes
4.	Were outcome assessors blinded to the treatment allocation?	Unclear
5.	Was the care provider blinded?	No
6.	Was the patient blinded?	No
7.	Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No
8.	Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
9.	Did the analysis include an ITT analysis?	Yes
	If so, was this appropriate?	Yes
	If so, were appropriate methods used to account for missing data?	Yes

a Answer: yes/no/unclear.

Appendix 7

List of excluded studies

The reasons for study exclusion were applied in the order given in the inclusion criteria worksheet (see *Appendix 4*). Studies may have been excluded on more than one criterion but only the primary reason is given.

Reason for exclusion: study design

Aguilera V, Rubin A, Benlloch S, Zamora PA, Ortiz C, Prieto M, *et al.* Systematic review of the treatment of established recurrent hepatitis C with pegylated interferon in combination with ribavirin. *Liver Transpl* 2008;**14**:S178.

Alberti A, Zehnter E, Lee S, Hadziyannis S, Zeuzem S, Rizzetto M, *et al.* Sustained virological response rates with peginterferon alpha-2a (40 kd) (PEGASYS®) plus ribavirin (COPEGUS®) in randomised controlled clinical trials are replicated in the clinical practice setting. *J Hepatol* 2007;**46**(Suppl. 1).

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Appendix 8

Net benefit framework

Cost-effectiveness decision rules and the incremental cost-effectiveness ratio

Standard decision rules for considering the cost-effectiveness of an intervention (I), compared with a given comparator (C), focus on the difference in effect ($\Delta E = E_I - E_C$ also referred to as the incremental effect) and the difference in cost ($\Delta C = C_I - C_C$ also referred to as the incremental cost). The decision rules are outlined using the cost-effectiveness plane as shown in *Figure 24*, below.

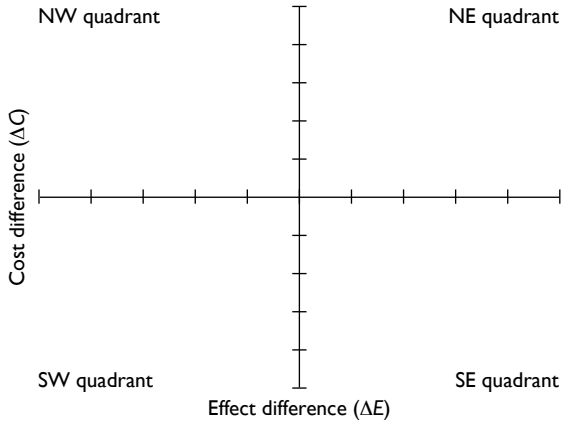

FIGURE 24 Cost-effectiveness plane for intervention (I) compared with comparator (C).

If the incremental cost is negative and the incremental effect is positive (SE quadrant), the intervention is unequivocally cost-effective (it is dominant, achieving better outcomes at lower cost).

If the incremental cost is positive and the incremental effect is negative (NW quadrant), the intervention is unequivocally not cost-effective (it is dominated, achieving poorer outcomes at higher cost).

If *both* the incremental cost and the incremental effect are negative (SW quadrant) or *both* the incremental cost and the incremental effect are positive (NE quadrant) no such unequivocal statements can be made. Determining whether the intervention is cost-effective depends on a threshold value (λ), defined as the maximum amount society is willing to pay for an incremental health gain or, equivalently, as the minimum amount society is willing to accept for foregoing an incremental health gain. The intervention would be regarded as cost-effective if its incremental cost-effectiveness ratio is lower than the threshold ($\Delta C/\Delta E < \lambda$) for ICERs in the NE quadrant or higher than the threshold ($\Delta C/\Delta E > \lambda$) for ICERs in the SW quadrant.

Cost-effectiveness decision rules and incremental net benefit

The inequalities ($\Delta C/\Delta E < \lambda$ for ICERs in the NE quadrant and $\Delta C/\Delta E > \lambda$ for ICERs in the SW quadrant) can be re-arranged to give equivalent inequalities on the cost scale (incremental net monetary benefit) or on the effect scale (incremental net health benefit) (see Briggs and colleagues 2006):

incremental net monetary benefit: $\lambda \times \Delta E - \Delta C > 0$

incremental net health benefit: $\Delta E - \frac{\Delta C}{\lambda} > 0$

One of the drawbacks of the incremental cost-effectiveness ratio is that the location of negative ICERs [whether they are in the SE (dominant) or NW (dominated) quadrant] cannot be determined without reference to other contextual information (the incremental cost and incremental effectiveness underlying the ratio or the quadrant of the cost-effectiveness plane). Similarly, positive ICERs cannot be interpreted (given that the decision rules depend on whether the ICER lies in the NE or the SW quadrant) without such additional information. In contrast, the incremental net benefit (regardless of the scale) provides an unambiguous decision rule, although this implies knowledge of the threshold value (λ), which has been a subject of considerable debate in the context of NICE decision making (see Appleby and colleagues 2007, McCabe and colleagues 2008, Raftery 2009 and Towse 2009). Current NICE methodological guidance suggests presenting expected net monetary health benefits using values of £20,000 and £30,000 per QALY for λ.

Example This report presents cost-effectiveness results for shortened treatment duration using peginterferon alfa-2a combination therapy in genotype 1 patients (see *Table 44*), peginterferon alfa-2a combination therapy in genotype 2 or 3 patients (see *Table 45*) and peginterferon alfa-2b combination therapy in genotype 1 patients (see *Table 50*). The table below presents these results along with the incremental net benefits.

For genotype 1 patients treated with peginterferon alfa-2a, the ICER is positive and ranges from approximately £35,000 to £65,000 per QALY gained. Without reference to the incremental cost and incremental QALY estimates we cannot determine which quadrant (NE or SW) the ICER is located in – therefore we do not know which cost-effectiveness decision rule to apply. However, the incremental net monetary benefits (or equivalently the incremental net health benefits) are positive at both suggested threshold values, suggesting that reduced duration of treatment is a cost-effective option for genotype 1 patients treated with peginterferon alfa-2a.

For genotype 1 patients treated with peginterferon alfa-2b and genotype 2 or 3 patients treated with peginterferon alfa-2a the ICER is negative. Again, without reference to the incremental cost and incremental QALY estimates we cannot determine which quadrant (NW or SE) the ICER is located in – therefore we do not know whether shortened treatment duration dominates or is dominated by standard duration. The incremental net benefits are positive at both suggested threshold values, suggesting that reduced duration of treatment is a cost-effective option in these patient groups.

Shortened treatment duration with peginterferon in different patient groups

The table below provides details of the incremental cost and outcome, ICERs and incremental net monetary (health) benefits for shortened treatment duration with peginterferon in different patient groups.

Treatment: patient group	RCT	Incremental		ICER (£ per QALY gained)	Incremental net benefit			
					Monetary		Health	
		Cost (£)	Outcome (QALYs)		λ = 20,000	λ = 30,000	λ = 20,000	λ = 30,000
PEG α-2a: genotype 1	Liu and colleagues[53]	–4807	–0.14	34,510	2007	607	0.10	0.02
	Yu and colleagues 2008[54]	–5212	–0.08	64,880	4526	4722	0.18	0.09
PEG α-2b: genotype 1	Berg and colleagues[59]	–8996	0.49	–18,359	18,796	23,696	0.94	0.79
PEG α-2a: genotype 2 or 3	Yu and colleagues[55]	–2107	0.08	–26,338	3707	4507	0.19	0.15
	von Wagner and colleagues 2008[54]	–3146	0.23	–13,678	4288	4176	0.39	0.33

PEG α, peginterferon alfa.

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Appendix 9

SVR estimates for re-treated, and for HCV/HIV co-infected, patients used in the SHTAC economic model

Re-treated patients

As explained in *Chapter 3* (*Methods of data analysis/synthesis*) of this report, no RCTs of re-treatment with peginterferon alfa and ribavirin following non-response to, or relapse from, a previous course of peginterferon alfa and ribavirin met the inclusion criteria for the systematic review of clinical effectiveness. This was because no RCTs used BSC as a comparator, and it was not possible to conduct an adjusted indirect comparison. Our search did identify one RCT (evaluating peginterferon alfa-2a) that met all of the criteria, with the exception that it had an active comparator (different regimens of peginterferon alfa-2a plus ribavirin).[88] For the purposes of economic modelling we have used the SVR reported for Group C of the trial (peginterferon alfa-2a 180 µg/week, plus ribavirin for 72 weeks) for genotype 1 patients (the SPC recommends 72 weeks re-treatment for genotype 1 patients).[42] For genotype non-1 patients SVRs were taken from Group D of the trial (peginterferon alfa-2a 180 µg/week, plus ribavirin for 48 weeks) (the SPC recommends 48 weeks re-treatment for genotype non-1 patients).

We did not identify any published RCTs of re-treatment with peginterferon alfa-2b plus ribavirin, irrespective of whether an active or inactive comparator was used. However, in order to model the cost-effectiveness of this drug we used SVRs from the currently unpublished EPIC3 study,[96] which was also used by Schering-Plough in their submission to NICE. EPIC3 is an uncontrolled study that evaluates peginterferon alfa-2b and ribavirin for 48 weeks in over 2000 patients who had failed to respond to, or relapsed on, previous treatment (around two-thirds had received non-peginterferon alfa).

For both peginterferon alfa-2a and 2b we assumed that no patients receiving only BSC would achieve an SVR. Caution is therefore necessary in the interpretation of the ICERs, given that they are not based on an adjusted indirect comparison.

HCV/HIV co-infected patients

Given that no RCTs of antiviral treatment in HCV/HIV co-infected patients met the inclusion criteria for our systematic review of clinical effectiveness, we have taken SVR estimates for patients treated with peginterferon alfa and ribavirin from two recent published systematic reviews in co-infected patients.[50,51] These reviews were identified from the search conducted for our clinical effectiveness systematic review. Both reviews comprise the same six RCTs in which peginterferon alfa plus ribavirin was compared to either peginterferon alfa monotherapy or to non-peginterferon alfa plus ribavirin. We have extracted and tabulated the SVRs for the individual RCTs presented in the systematic reviews according to type of peginterferon alfa (2a or 2b) and genotype (see tables below). As it has not been possible to perform an adjusted indirect comparison between peginterferon alfa and ribavirin and BSC [as explained in *Chapter 3*

(*Methods of data analysis/synthesis*], we have assumed that no patients receiving only BSC will achieve an SVR. Again, caution is therefore necessary in the interpretation of the ICERs given that they are based upon an unadjusted indirect comparison.

Overall SVRs for HCV/HIV co-infected patients

Study	No. with SVR (%)	Total no. of patients
Peginterferon α-2a		
Chung and colleagues (2004)[118]	18 (27)	66
Torriani and colleagues (2004)[66]	116 (40)	289
Combined	**134 (38)**	**355**
Peginterferon α-2b		
Carrat and colleagues (2004)[116]	56 (27)	205
Laguno and colleagues (2004)[95]	23 (44)	52
Crespo and colleagues (2007)[119]	33 (55)	60
Cargnel and colleagues (2005)[120]	15 (22)	69
Combined	**127 (33)**	**386**

Genotypes 1 and 4

Study	No. with SVR (%)	Total no. of patients
Peginterferon α-2a		
Chung and colleagues (2004)[118]	7 (14)	51
Torriani and colleagues (2004)[66]	57 (30)	194
Combined	**64 (26)**	**245**
Peginterferon α-2b		
Carrat and colleagues (2004)[116]	21 (17)	125
Laguno and colleagues (2004)[95]	12 (38)	32
Crespo and colleagues (2007)[119]	18 (46)	39
Cargnel and colleagues (2005)[120]	4 (11)	37
Combined	**55 (24)**	**233**

Genotypes 2 and 3

Study	No. with SVR (%)	Total no. patients
Peginterferon α-2a		
Chung and colleagues (2004)[118]	NA	NA
Torriani and colleagues (2004)[66]	59 (62)	95
Combined	**59 (62)**	**95**
Peginterferon α-2b		
Carrat and colleagues (2004)[116]	35 (44)	80
Laguno and colleagues (2004)[95]	10 (57)	19
Crespo and colleagues (2007)[119]	15 (71)	21
Cargnel and colleagues (2005)[120]	11 (34)	32
Combined	**71 (47)**	**152**

Data for the Cargnel and colleagues study[120] have been added in, but these were not used in the respective meta-analyses of peginterferon alfa and ribavirin compared with non-peginterferon alfa by Kim and colleagues[51] and Zhao and colleagues,[50] as the study compared peginterferon alfa and ribavirin with peginterferon alfa monotherapy. Also data for the Chung and colleagues study[118] for genotype 1 and 4 patients was not used in the meta-analysis by Kim and colleagues,[51] but have been added in here. Therefore, the combined SVR results presented below are not strictly comparable with those in the published meta-analyses.

Appendix 10

Variables and probability distributions used in the probabilistic model

In the PSA, transition probabilities and utilities are sampled from beta distributions and costs are sampled from gamma distributions.[121] Parameters for sampling distributions were derived from point estimate and SEs for each variable, using the 'method of moments'.[121]

Name	Distribution	Alfa	Beta
Transition probabilities			
Mild-to-moderate chronic HCV	Beta	38.08594	1485.35156
Moderate chronic HCV to CC		26.90504	700.25822
Compensated to DC		14.61681	360.17319
CC to HCC		1.93256	136.10744
DC to HCC		1.93256	136.10744
DC excess mortality		147.03000	983.97000
HCC excess mortality		117.10333	155.23000
Utilities			
Utility of SVR (from mild chronic HCV)	Beta	65.86776	14.45878
Utility of SVR (from moderate chronic HCV)		58.06080	22.57920
Utility of SVR (from CC) – by assumption		58.04760	37.11240
Utility of mild chronic HCV		521.23750	155.69432
Utility of moderate chronic HCV		168.24614	86.67226
Utility of CC		47.10208	38.53806
Utility of DC		123.75000	151.25000
Utility of HCC		123.75000	151.25000
Utility of liver transplant		123.75000	151.25000
Utility of post liver transplant		59.25480	29.18520
Health-state costs			
Cost of SVR state	Gamma	28.81409	8.98866
Cost of mild chronic HCV		25.69952	5.36975
Cost of moderate chronic HCV		88.85025	8.06976
Cost of CC		24.23423	46.95836
Cost of DC		36.03281	253.13041
Cost of HCC		18.10811	448.80449
Cost of liver transplant		89.75357	304.50042
Cost of care in year of liver transplant		13.77880	686.41683
Cost of care in years after liver transplant		15.21890	91.00529

In the PSA treatment effects (probability of SVR and, where relevant, EVR) are sampled from beta distributions. The parameters of the sampling distributions are the number of events of interest (EVR or SVR) in the relevant population.[121]

Treatment effects	Distribution	Events	Population
Shortened treatment duration peginterferon α-2a			
Liu and colleagues[53]			
SVR – standard duration	Beta	57	58
SVR – shortened duration		69	74
Yu and colleagues 2007[55]			
SVR – standard duration	Beta	24	25
SVR – shortened duration		27	29
Yu and colleagues 2008[54]			
SVR – standard duration	Beta	85	88
SVR – shortened duration		43	44
Yu and colleagues 2007[55]			
SVR – standard duration	Beta	27	31
SVR – shortened duration		33	35
Shortened treatment duration peginterferon α-2b			
SVR – standard duration	Beta	8	19
SVR – shortened duration		16	28
Re-treatment with peginterferon α-2a			
EVR – genotype 1	Beta	21	142
SVR – genotype 1		18	21
EVR – genotype non-1		10	29
SVR – genotype non-1		6	10
Re-treatment with peginterferon α-2b			
EVR – genotype 1	Beta	333	1121
SVR – genotype 1		162	333
EVR – genotype non-1		162	206
SVR – genotype non-1		117	162
HCV/HIV co-infected treated with peginterferon α-2a			
SVR – genotypes 1 and 4	Beta	64	245
SVR – genotypes 2 and 3		59	95
HCV/HIV co-infected treated with peginterferon α-2b			
SVR – genotypes 1 and 4	Beta	55	233
SVR – genotypes 2 and 3		71	152

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We look forward to hearing from you.

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