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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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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions 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)

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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. 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 RNA six months after cessation of treatment. Since these recommendations, there have been extensions to the licenses for both peginterferons to allow patients, who have a low viral load (LVL) and achieve a rapid virological response (RVR) at four 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/HIV co-infection to receive treatment. This review focuses specifically on these new indications.

Objectives

To assess the clinical and cost-effectiveness of peginterferon alfa and 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 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. Manufacturer submissions (MS) 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 unable to tolerate ribavirin) compared to shortened duration courses of combination therapy (24 weeks for genotype 1; 16 weeks for genotype 2/3) 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 due to differences in the drug regimens, and because outcome data were based on relatively small sub-groups 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 α-2a and peginterferon α-2b in sub-groups of adults who: were eligible for a shortened duration of treatment with peginterferon alfa; had failed to respond 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 NHS and personal social services. The short term outcome of treatment was sustained viral response (SVR). The model extrapolated the impact of SVR on life expectancy, quality-adjusted life expectancy and lifetime costs for each sub-group of patients with HCV. Published quality of life 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 anti-viral treatment was estimated from clinical guidelines and advice from clinical practitioners. Drug costs were taken from the British National Formulary. 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 2,400 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 eligible for shortened treatment duration. No RCTs comparing peginterferon alfa with or without ribavirin compared to 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 genotype 2/3 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 good overall.

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

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

In the one trial reporting virological relapse rates in the sub-group 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 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 quality of life 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 anti-viral treatment strategies for patients who were co-infected with HCV/HIV. Both evaluations indicated that HCV anti-viral treatment was associated with gains in life expectancy for HCV/HIV co-infected patients. A systematic search for published studies of quality of life found no relevant studies.

Roche submitted a dossier in support of peginterferon α-2a combined with ribavirin in three sub-groups 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 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 £2,719 for genotypes 2 and 3 with LVL and RVR. For non-responders, comparing re-treatment to BSC, the ICERs were £3,334 and £809 per QALY gained for genotypes 1 + 4 and 2 + 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-pegylated interferon and ribavirin combination therapy.

Schering-Plough submitted a dossier in support of peginterferon alfa-2b combined with ribavirin in two of the three sub-groups 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 to BSC, the overall ICER in non-responders/relapsers was £4,387 per QALY gained. In genotypes 1 and 4 the ICER was £7,177 and in genotypes 2 and 3 it was £783 per QALY gained. The ICER for peginterferon alfa-2b in HCV/HIV patients compared to BSC was £1,637 in genotypes 1 and 4 and £403 in patients with genotypes 2 and 3. The ICER for all patients was £1,077.

In our base case analysis, SVRs for peginterferon α-2a from two trials included in our systematic review of clinical-effectiveness were used to model cost-effectiveness in genotype 1 patients 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 α-2b dominated standard treatment.

In genotype 1 and genotype non-1 patients re-treated with peginterferon α-2a the ICERs were £9,169 and £2,294 respectively. In genotype 1 + 4 patients re-treated with peginterferon α-2b the ICER was £7,681, while re-treatment dominated BSC for genotype 2 + 3 patients. In HCV/HIV co-infected patients receiving peginterferon α-2a the ICER was £7,941 per QALY gained in genotypes 1 and 4 patients whilst peginterferon α-2a dominated BSC in genotypes 2 and 3. In co-infected patients receiving peginterferon α-2b the ICER was £11,806 in genotypes 1 and 4, and £2,161 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 sub-groups of varying sizes of the randomised patients and are likely to be underpowered. The results of the trials in these sub-groups 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 sub-groups 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 (genotype 2/3), or 24 weeks (genotype 1), without compromising SVR rates. However, the cost-effectiveness analyses indicate that a judgment 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 sub-groups 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 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 naïve and treatment-experienced people with chronic HCV.

LIST OF ABBREVIATIONS

ALT	Alanine aminotransferase
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CrI	Credible interval
DSA	Deterministic sensitivity analysis
EVR	Early virological response
EOT	End of treatment (virological response)
HAART	Highly Active Antiretroviral Therapy
HBV	Hepatitis B virus
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
ICER	Incremental Cost-effectiveness Ratio
IDU	Injecting drug user
IFN	Interferon alfa (non-pegylated)
IU	International units
LVL	Low viral load
mcg, µg	Micrograms
ml	Millilitre
mm	Millimetre
MS	Manufacturers' submission
MSM	Men who have sex with men
NICE	National Institute for Health and Clinical Excellence
PEG α	Pegylated interferon alfa
QALY	Quality Adjusted Life Year
QoL	Quality of life
PSA	Probabilistic sensitivity analysis
PSS	Personal and social services
RBV	Ribavirin
RCT	Randomised controlled trial
RNA	Ribonucleic acid
RR	Relative Risk / Risk Ratio
RVR	Rapid virological response
SPC	Summary of product characteristics
SVR	Sustained virological response
TA	Technology Appraisal
TTO	Time trade-off
ULN	Upper limit of normal
wk	Week

BACKGROUND

1.1 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 Section 1.3 and Section 1.4).

There are two main phases of infection: acute and chronic. Acute HCV refers to the period immediately after HCV infection, whilst chronic HCV (the focus of this report) is defined as infection persisting for more than six months. Of those exposed to HCV, approximately 20% will clear the virus spontaneously whilst 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 Section 1.1.3). 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, they can cause a significant decrease in quality of life in others 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.

1.1.1 Aetiology

HCV 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 to baby transmission, occupational exposure (e.g. via needle stick 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 traditionally

been thought 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 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]

1.1.2 Epidemiology

1.1.2.1 Prevalence

The estimated global prevalence of chronic HCV is around 2-3%, corresponding to about 130-170 million people.[1,8] In England & Wales the HPA[3] estimate that, based on statistical model data for the year 2003, around 191,000 (95% Credible interval, CrI 124,00 – 311,00) people aged 15-59 years are HCV anti-body positive, with 142,000 people chronically infected; a prevalence of 0.44% (95% CrI 0.29 – 0.72) in this age group.

Prevalence estimates vary geographically in England and Wales, with highest numbers of laboratory reports (from public health and 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 whilst overseas, notably Pakistan.[3]

Evidence suggests varying rates of HCV in people with HIV infection. For example, Mohsen and colleagues (2002)[10] reviewed the international literature on the epidemiology of HCV/HCV co-infected patients. They included 12 HCV sero-prevalence studies carried out in HIV-1 infected people in Europe and the United States. 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 3,688 in Wales (from 1996).[3] It is thought that a proportion of those 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]

1.1.2.2 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 available yet, but recent studies in IDUs suggest 3-42% of susceptible injectors become infected each year.[3] The HPA report that the number of laboratory confirmed diagnoses of HCV in England and Wales in 2007 was 7,540, 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 has 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 US have been reported in recent years.[12] A study of Genito-Urinary 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 to June 2006.[7] The prevalence of HCV in HIV-positive MSM is estimated to be between 4 and 11.5%.[12]

1.1.3 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 that 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 stage (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 Histological Activity index (HAI),[15] and the METAVIR system.[16] The Ishak system, for example, classifies mild HCV as a fibrosis score of $\leq$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 on anti-viral treatment for mild HCV for further detail on liver biopsy classification systems).[17]

Cirrhosis can develop rapidly, within 1-2 years of exposure (though this is rare), but more usually develops slowly, over 2-3 decades. A recent Markov modelling study 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.[18] The estimates were highly sensitive to the type of cohort used, with lower estimates from the HCV National Register look-back cohort, comprising individuals identified from blood screening and donor surveillance schemes, and highest 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 to 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 3,705 (95% credible interval CrI 2820-4975) in 2005 to 7,550 (95% CrI 5120-116400) in 2015.[20]

Patients with HCV-related cirrhosis are at risk of developing hepatacellular 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 1,150 (95% CrI 1055-1250) in 2005 to 2,540 (95% CrI 2035-3310) 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 2,313 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 developed cirrhosis over a 20 year period compared to 6% of those infected between 31 and 40 years, 37% infected between 41 and 50 years and 63% infected after the age of 50. HCV genotypes and HCV RNA viral load, although important in governing the effectiveness of treatment regimens (see Section 1.3.2), 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 (2003)[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 and 0.13 in HCV mono-infected patients respectively (p=0.01). This equates to an estimated time 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 independently related to fibrosis progression. A retrospective analysis by Poynard and colleagues (2003)[27] of 4,852 patients with chronic liver disease of a variety of causes found that HCV/HIV co-infection was associated with the fastest fibrosis progression, compared to 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 comparable to that of HCV mono-infected people,[12] though a systematic review of natural history studies in co-infected patients concluded that this was not the necessarily 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, whilst there has been an increase in liver 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]

1.2 Diagnosis

Presence of HCV infection may be detected through the identification of antibodies using enzyme linked immunosorbant assays (ELISA), and then confirmed through the identification of HCV RNA in serum.[32] The latter can be done using sensitive molecular assays such as polymerase chain reaction (PCR). A detectable HCV viral load of 50 International Units / millilitre (IU/ml) or above is generally considered indicative of infection, though 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 Section 1.3.2). Alanine aminotransferase (ALT) biochemical tests are also used to indicate potential HCV-related liver damage, though 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 likely commence anti-viral 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 inter-observer reliability between pathologists, and the suggestion that it may discourage some patients from presenting for assessment. Furthermore, guidance from organisations such as 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 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 has not yet been appraised at the policy level in England and Wales.

1.3 Current service provision

1.3.1 Anti-viral treatment

The majority of people with chronic HCV will not clear the virus spontaneously and will need to be assessed for possible anti-viral 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 anti-viral treatment.

The primary aim of treatment is to clear the virus from the blood, and success is usually taken to be a sustained viral 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, though 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 RCTs in which the effects of anti-viral treatment, in terms of SVR, has been correlated with long-term clinical outcomes. The exception is for cirrhotic patients in which 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 anti-viral 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 whose mechanism of action is to assist the immune response by inhibiting viral replication. Two forms are available:

peginterferon α-2a (Pegasys, Roche Products) and peginterferon α-2b (ViraferonPeg, Schering-Plough). Ribavirin is a synthetic nucleoside analogue which is available in three forms: Copegus (Roche Products), Rebetol (Schering-Plough) and Ribavirin Teva (Teva UK Ltd.). Copegus is licensed for combination therapy only with peginterferon α-2a, whilst the latter two drugs are licensed for combination therapy only with peginterferon α-2b.

The current NICE guidance (Technology Appraisal (TA) 106, [38] an extension of TA 75[33]) recommends combination therapy with ribavirin and either peginterferon α-2a or peginterferon α-2b for adult patients with chronic HCV, regardless of disease severity. Monotherapy with peginterferon α-2a or peginterferon α-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 viral response to treatment. Treatment is currently restricted to:

- patients who are treatment naïve
- patients who have previously been treated with non-peginterferon alfa combination therapy or monotherapy
- patients who have previously been treated with peginterferon alfa monotherapy but didn't respond or subsequently relapsed.

It is not thought that there are substantial variations in practice across the country in terms of anti-viral treatment, though 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 are discussed in the following sub-sections.

1.3.2 Shortening the course of treatment

In recent years, one of the key aims of the management of HCV is to maximise the likelihood of an SVR whilst minimising potential adverse effects of treatment. The adverse effects associated with interferon based anti-viral 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 and 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 early viral response (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 that 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 that have responded.

Recently there has been a focus on identifying responders earlier than 12 weeks. A rapid virological response (RVR) is measured at week four 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 (LVL) 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 α-2a and peginterferon α-2b consider LVL as being HCV RNA $\leq$800,000 IU/ml, and <600,000 IU/ml, respectively.[42,43]

1.3.3 Re-treatment of non-responders and relapsers

Given the fact that, on average, SVRs are only achieved by between 50 and 60% of patients receiving anti-viral 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 anti-viral treatment. A relapser is defined as a patient who achieves loss of detectable HCV RNA during treatment, but in whom HCV RNA reappears either whilst 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 Section 1.3.2).[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.

1.3.4 Treatment of HCV and 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 Section 1.1.3). For example, treatment decisions need to take into account any possible drug interactions between HCV anti-viral medication and HAART (e.g. didanosine which is contraindicated in co-infected patients taking anti-viral 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 anti-viral 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 anti-viral treatment for this group in common with that for HCV mono-infected people.[33,38]

1.4 Description of technology under assessment

The intervention under assessment in this report is peginterferon α-2a and α-2b in combination with ribavirin (or as monotherapy if ribavirin is contra-indicated). Peginterferon α-2a was licensed in June 2002 with extensions to the license granted in June 2007. The recommended dose is 180 micrograms (μg) once per week, administered subcutaneously, for 16, 24 or 48 weeks dependent on genotype, baseline viral load and treatment response. Peginterferon α-2b was licensed in February 2002 with extensions to the license granted in May 2005. The recommended dose is 1.5μg/kg bodyweight once per week, administered subcutaneously, for 24 or 48 weeks dependant 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 800mg to 1400mg taken orally each day in two divided doses (200mg capsules), with the dose depending on the patient's bodyweight. The dose of Copegus also varies according to genotype (800mg per day for genotype 2/3 and 1000-1200mg per day (depending on body weight, 1000mg for weight <75 kg and 1200mg 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 naïve or may have failed previous monotherapy or combination treatment.

For peginterferon α-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 four weeks should receive 24 weeks treatment. The license extensions allow genotype 1 patients with LVL, an RVR and undetectable HCV RNA at wk 24 to complete treatment at week 24 rather than receive the standard 48 weeks. It also allows genotype 2/3 patients with both LVL (≤800,000 IU/ml), a n RVR and undetectable HCV RNA at week 16 to finish treatment at week 16 rather than receive the standard 24 weeks. 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 α-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. License extensions permit genotype 1 patients with LVL (< 600,000 IU/ml) and an RVR and undetectable HCV RNA at week 24 to receive 24 rather than 48 weeks treatment. The licence does not, however, permit shorter courses of treatment in genotype 2/3 or 4 patients. Patients receiving peginterferon monotherapy who achieve an EVR should continue treatment for another three months. Extension of treatment to one year should be based on prognostic factors such as age and genotype.

For both peginterferon α-2a and α-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 Summary of Product Characteristics (SPC).[42,43]

In terms of costs, a 180µg prefilled syringe of peginterferon α-2a (the recommended weekly dose) costs £126.91. A 168 x 200mg tab pack of ribavirin (Copegus) costs £444.43. The weekly cost of Copegus would be £111 for genotype 1 (based on 1200mg per day for an average body weight of 79kg) and £74 for genotype 2/3 (based on 800mg per day for an average body weight of 79kg). A 120µg prefilled injection pen of peginterferon α-2b costs £162.60. This would be the weekly cost for an average patient weighing 79kg (1.5µg per kg). A 168 tab x 200mg pack of ribavirin (Rebetol) costs £327. The weekly cost of for Rebetol would be £68 based on 1000mg per day for an average body weight of 79kg. All costs are from the British National Formulary, September 2009.[47] (see Section 5.3.5.3 for full details of the drug costs estimated in our independent economic evaluation).

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 α-2a and α-2b. This health technology assessment

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.

2.1 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 contra-indicated. The population of interest is adult patients with chronic HCV infection in one or more of the following patient groups: (i) those who meet the licensed criteria for receiving shortened courses of combination therapy; (ii) those who have been previously treated with peginterferon alfa and ribavirin in combination and who either did not respond or who responded but relapsed, and (iii) those who 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, six 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.

2.2 Overall aims and objectives of assessment

The aim of this health technology assessment 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.

3 METHODS

The *a priori* methods for systematically reviewing the evidence of clinical- and cost-effectiveness were described in a research protocol (Appendix 1) which was sent to experts for comment. Minor amendments were made as appropriate but no comments were received which identified specific problems with the methods of the review. The methods of the SHTAC economic evaluation can be seen in Section 5.3.

3.1 Identification of studies

A sensitive search strategy was developed and refined by an experienced information scientist and was based upon that employed 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 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
- CRD (University of York) databases: Database of Abstracts of Reviews of Effectiveness (DARE), NHS Economic Evaluation Database (NHS EED) and 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) & Conference Proceedings Citation Index - Science (CPCI) (ISI Web of Knowledge)
- Biosis Previews (ISI Web of Knowledge)
- NIHR-Clinical Research Network Portfolio
- Clinical Trials.gov
- Current Controlled Trials.

Bibliographies of retrieved papers were screened for relevant studies, and the manufacturers' submissions (MS) to NICE were assessed for any additional studies (see Appendix 3 for a critique of the clinical-effectiveness section of the MS, and Section 5.2 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 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 Hepatitis Co-infection workshop
- Health Protection Agency
- Hepatitis C Trust

3.2 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 re-screened 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.

3.2.1 Inclusion criteria

Study design

RCTs were included for the clinical-effectiveness review. Trials published as abstracts or conference presentations from 2007 onwards were only included 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 of ribavirin and either peginterferon α-2a or peginterferon α-2b
- Peginterferon α-2a or peginterferon α-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).

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
- people with HCV/HIV co-infection
- 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 LVL[†] at the start of treatment and an RVR (defined as HCV RNA undetectable by week 4) - shortened course of 16 weeks;*
  - patients with genotype 1 with LVL[†] and an RVR (defined as HCV RNA undetectable by week 4 and at week 24) - shortened course of 24 weeks;
  - patients with genotype 4 with an RVR (defined as HCV RNA undetectable by week 4 and at week 24) - shortened course of 24 weeks.*

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

Outcomes

Studies had to report SVR (defined as undetectable HCV RNA at least six 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
- health-related quality of life
- cost-effectiveness (incremental cost per life year gained) or cost-utility (incremental cost per quality adjusted life year gained)

3.2.2 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 the Centre for Reviews and Dissemination (CRD)[49] (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.

3.3 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 due to differences in the drug regimens and also because the population of interest (i.e. patients with LVL and RVR) were often sub-groups of the main treatment arms. Any meta-analyses would therefore compromise 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 section, we did not identify any such studies from our database of RCTs of both pegylated 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 anti-viral 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.

4 CLINICAL EFFECTIVENESS

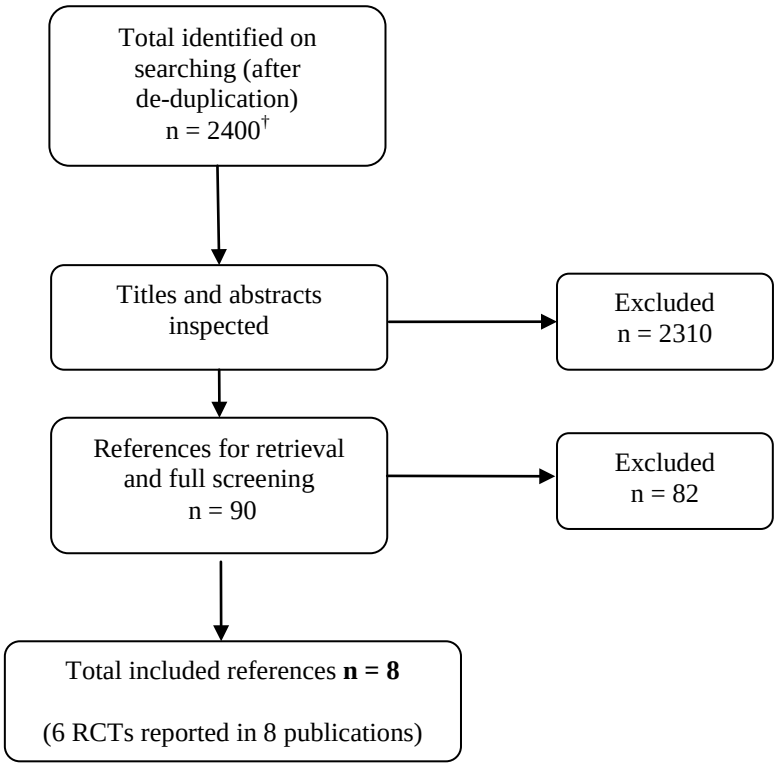
4.1 Results

4.1.1 Quantity and quality of research available

Literature searches identified 1,317 references, after the removal of duplicates. A further 1,389 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 2,400. Following initial screening of titles and abstracts, 2,310 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 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 Section 3.2.1). No RCTs comparing peginterferon alfa with or without ribavirin compared to 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 plus ribavirin versus non-peginterferon alfa plus ribavirin) but these did not meet the inclusion criteria for the review, which was based on the scope of the appraisal issued by NICE.[61]

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=2,706); further de-duplication left n=2,400 for screening.

The remainder of Section 4 describes the six trials in patients eligible for shortened courses of treatment.

4.1.2 Description of the included trials

The key characteristics of the RCTs are shown in Table 1. Four of the included studies evaluated peginterferon α-2a in combination with ribavirin,[53-56] one trial (Berg and colleagues[59]) evaluated peginterferon α-2b and ribavirin, and one trial evaluated peginterferon α-2a or peginterferon α-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 α-2a was the same in all the trials (180 µg/week subcutaneously), as was the dose of peginterferon α-2b (1.5 µg/kg/week). Ribavirin was administered orally according to bodyweight at a dose of 1,000 mg/day for patients ≤75kg and 1,200 mg/day for patients >75kg in four studies,[52-55] or 800 mg/day for patients ≤65kg, 1,000 mg/day for patients 65 - 85kg and 1,200 mg/day for patients >85kg in one study.[56] Berg and colleagues[59] reported only that patients received 800 to 1,400 mg/d of ribavirin and it is assumed that the dose was administered according to bodyweight. 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 α-2a + ribavirin combination treatment (800 mg/day for genotype 2/3[42,62]) due 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 week 4, week 8 and week 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 week 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 (2007)[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 genotype 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 versus 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 sub-group of patients with LVL and RVR. The two trials in genotype 2/3 patients[55,56] used a cut off HCV RNA level of ≤800,000 IU/ml to differentiate low and high viral load. The Berg and colleagues trial in genotype 1 patients[59] 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 α-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 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 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] whilst Liu and colleagues[53] used a lower limit of <25 IU/ml. In the Berg and colleagues trial,[59] HCV RNA negatitivity 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 multi-centre trials (ranging from four to nineteen 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 trial 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 the trials were based on middle-aged (mean age range 39-53 years) adult patients, with the proportion of male participants ranging from 55-73%. Patients were treatment-naïve 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 whilst approximately 20% were infected by blood transfusion and 8% 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% to 87%), with a 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≥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] 2[55] or 2 or 3.[56]

Exclusion criteria were similar across the included trials. All six excluded patients with significant co-morbidities 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 the trials stipulated certain laboratory readings in their inclusion/exclusion criteria, most of which are related to conditions which are consistent with decompensated liver cirrhosis such as thrombocytopenia, anaemia and neutropenia. Patients were required to have a neutrophil count >1,500 cells mm^{-3}, a platelet count ranging from at least 70,000 cells mm^{-3} to at least 90,000 cells mm^{-3}, haemoglobin levels of ≥11 to 12 g/dl for women and ≥12 to 13 g/dl for men and creatinine <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 health-related quality of life.

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 are 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.

Table 1 Key characteristics of included trials ordered by genotype

Study	Methods	Key inclusion criteria	Key patient characteristics	Outcomes
Berg *et al.*, 2009[59]	*Design*: open-label, multi-centre RCT *Number 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 48wks *vs* PEG α-2b + RBV for 18, 24, 30, 36, 42 or 48wks *Follow-up*: 24 weeks after treatment cessation *No. participants*: n=433	*Inclusion criteria*: • Treatment naïve adults with compensated chronic HCV, genotype 1 • Anti-HCV positive • HCV RNA > 1,000 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 Gp 1, 5.7 Gp 2 • Mean serum ALT xULN, IU/L: 2.6 Gp 1, 2.6 Gp 2 • Fibrosis stage 0-2: 87% Gp 1, 85% Gp 2 • Genotype 1: 100% • Mean age: 42 years • Gender: 55% male • Mode of infection: not reported • Ethnicity: not reported	*Primary outcomes*: • SVR *Secondary outcomes*: • Biochemical response* • On-treatment virological response (RVR, EOT) • Relapse rate • Adverse events
Mangia *et al.*, 2008[52]	*Design*: multi-centre RCT *Number of centres*: 11 *Country*: Italy *Sponsor*: not reported *Interventions*: PEG α-2a or PEG α-2b + RBV for 48wks *vs* PEG α-2a or PEG α-2b + RBV for 24, 48 or 72wks *Follow-up*: 24 weeks after treatment cessation *No. participants*: n=696	*Inclusion criteria*: • Treatment naïve 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	• Serum HCV RNA <400,000 IU/ml: 26% Gp 1, 22% Gp 2 • Serum ALT ≥3 ULN: 19% Gp 1, 16% Gp 2 • Fibrosis stage 0-2: 62% Gp 1, 65% Gp 2 • Genotype 1a: 9%, 1b: 91% • Mean age: 52 years • Gender: 56% male • Mode of infection: blood transfusion 21%, drug abuse 7%, unknown 72%	*Primary outcomes*: • SVR *Secondary outcomes*: • RVR • EOT virologic response • SVR according to virologic response at wks 4, 8 & 12

		• Creatinine < 1.5 mg/dl	• Ethnicity: not reported • Treatment: PEG α-2a 46% Gp 1, 49% Gp 2; PEG α-2b 53% Gp 1, 51% Gp 2	• Relapse rate • Adverse events
Liu *et al.*, 2008[53] and Liu *et al*., 2008 abstract[57]	*Design*: multi-centre RCT *Number 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 wks *vs* PEG α-2a + RBV for 48 wks *Follow-up*: 24 weeks after treatment cessation *No. participants*: n=308	*Inclusion criteria*: • Treatment naïve 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 Gp 1, 5.8 Gp 2 • Mean serum ALT x ULN: 3.2 Gp 1, 3.0 Gp 2 • Fibrosis score ≥3: 77% • Genotype 1a: 2%, 1b: 94%, 1a and 1b: 4% • Mean age: 54 years • Gender: 57% male • Mode of infection: not reported • Ethnicity: 100% Asian	*Primary outcomes*: • SVR *Secondary outcomes*: • RVR • EVR • EOT virologic response • Relapse rate • Biochemical response • Histologic response • Adverse events
Yu *et al*., 2008[54] and Yu *et al*., 2007 abstract[58]	*Design*: open-label, multi-centre RCT *Number of centres*: 4 *Country*: Taiwan *Sponsor*: Taiwan Liver Research Foundation *Interventions*: PEG α-2a + RBV for 24 wks *vs* PEG α-2a + RBV for 48 wks *Follow-up*: 24 weeks after treatment cessation *No. participants*: n=200	• Treatment naïve 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	• Mean viral load (log_{10} IU/ml): 5.43 Gp 1, 5.66 Gp 2 • Serum HCV RNA <400,000 IU/ml: 55% • Serum ALT IU/L: 156 Gp 1, 137 Gp 2 • Fibrosis score 0-2: 75% Gp 1, 81% Gp 2 • Genotype 2: 100% • Mean age: 49 years • Gender: 57% male • Mode of infection: not reported • Ethnicity: not reported	*Primary outcomes*: • SVR *Secondary outcomes*: • RVR • EVR • EOT virologic response • Relapse rate • Adverse events

		• Creatinine < 1.5 mg/dl		
Yu *et al*., 2007[55]	*Design*: open-label, multi-centre RCT *Number of centres*: 4 *Country*: Taiwan *Sponsor*: Taiwan Liver Research Foundation *Interventions*: PEG α-2a + RBV for 24 wks *vs* PEG α-2a + RBV for 16 wks *Follow-up*: 24 weeks after treatment cessation *No. participants*: n=150	• Treatment naïve 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 x ULN for ≤2 measurements within 6 months before study entry • Neutrophils > 1500 mm^{-3} • Platelets > 9 x 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 Gp 1, 4.98 Gp 2 • Serum ALT IU/L: 108.9 Gp 1, 107 Gp 2 • Fibrosis score 0-2: 80% Gp 1, 78% Gp 2 • Genotype 2: 100% • Mean age: 50 years • Gender: 60% male • Mode of infection: not reported • Ethnicity: 100% Asian (Taiwanese)	*Primary outcomes*: • SVR *Secondary outcomes*: • RVR • EOT virologic response • Relapse rate • Adverse events
von Wagner *et al*., 2005[56]	*Design*: multi-centre, phase IIIb RCT *Number of centres*: 6 *Country*: Germany *Sponsor*: Hoffmann-La Roche and German Hepatitis Network of Competence (Hep-Net) *Interventions*: PEG α-2a + RBV for 16 wks *vs* PEG α-2a + RBV for 24 wks (RVR) *vs* PEG α-2a + RBV for 24 wks (no RVR)	• Treatment naïve 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	• Mean viral load (log_{10} IU/ml): 5.8 Gp 1, 5.8 Gp 2 • Serum ALT xULN IU/L: 2.8 Gp 1, 2.8 Gp 2 • Mean fibrosis score: 1.6 Gp 1, 1.6 Gp 2 • Genotype 2: 27%, genotype 3: 73% • Mean age: 38 years • Gender: 65% male • Mode of infection: not reported • Ethnicity: not reported	*Primary outcomes*: • SVR *Secondary outcomes*: • RVR • EOT virologic response • Biochemical response • Adverse events

	Follow-up: 24 weeks after treatment cessation *No. participants*: n=142	• Platelets >90,000/µL • Hb ≥12 g/dl for women, ≥13 for men		

PEG, peginterferon; RBV, ribavirin; wks, weeks; Hb, haemoglobin; ULN, upper limit of normal; Gp, group; SVR, sustained virological response; RVR, rapid virological response; EVR, early virological response; EOT, end of treatment virological response; *reported by the authors as a secondary outcome but results not presented in the publication.

Quality assessment of included studies

The methodological quality of reporting in the included studies was assessed using criteria set by the Centre for Reviews and Dissemination (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, whilst 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 virologic 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 care-givers 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 drop-outs 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 Berg and colleagues[59] where sustained biuochemical response was reported by the authors as a secondary outcome but no results were presented in the publication. All six RCTs undertook an appropriate intention-to-treat (ITT) data analysis for the primary efficacy outcome, although appropriate methods were used to account for missing data in only three trials.[54-56] All 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 sub-groups (such as those with RVR and LVL), and therefore these results in the following sections should be interpreted with caution.

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*	Yes*	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 drop-outs	No	No	No	No	No	No
More outcomes measured than reported	Yes	No	No	No	No	No
ITT analysis included - appropriate - missing data accounted for	Yes Unclear Unclear	Yes Yes Unclear	Yes Yes Unclear	Yes Yes Yes	Yes Yes Yes	Yes Yes Yes

*baseline characteristics similar for group 1 vs group 2 as a whole, but unclear for group 1 vs 24 week subset

4.1.3 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 sub-group of patients with an RVR and LVL, where reported. Results presented in the tables are ordered by genotype.

4.1.3.1 Sustained virological response

SVR 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]

SVR was the primary outcome in all six included RCTs. Four of the trials[52-54,56] separately reported SVR in the sub-group of patients who achieved an RVR and had LVL at baseline, which is the patient sub-group meeting the licensed criteria for receiving shortened courses of combination therapy (Table 3). Yu and colleagues (2007)[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 since the mean baseline viral load was

Table 3 Sustained virological response in the sub-group of patients with an RVR and LVL

Study details	Group 1	Group 2	*p*-value
Genotype 1			
Berg *et al*.[59]	**PEG α-2b + RBV [a] 48 weeks, n=225**	**PEG α-2b + RBV 24 weeks, n=28[b]**	
SVR by RVR, % (n/N)	42 (8/19)	57 (16/28)	*p*=not reported
Mangia *et al*. [52]	**PEG α-2a or α-2b + RBV 48 wks, n=237**	**PEG α-2a or α-2b + RBV 24 wks, n=123[c]**	
SVR by RVR and baseline viral load, % (n/N):			
<400,000 IU/ml	83.3 (20/24)	84.4 (38/45)	*p*=0.83
≥400,000 IU/ml	86.8 (33/38)	73.1 (57/78)	*p*=0.14
Liu *et al*. [53]	**PEG α-2a + RBV 48 wks, n=154**	**PEG α-2a + RBV 24 wks, n=154**	**p-value**
SVR by RVR and baseline viral load, % (n):			
<400,000 IU/ml	100 (42)	94 (49)	*p*=0.25
<600,000 IU/ml	100 (50)	93 (61)	*p*=0.13
<800,000 IU/ml	100 (57)	94 (69)	*p*=0.13
<1,000,000 IU/ml	100 (61)	92 (71)	*p*=0.03
Yu *et al*., 2008[54]	**PEG α-2a + RBV 48 wks, n=100**	**PEG α-2a + RBV 24 wk, n=100**	**p-value**
SVR by RVR and baseline viral load, % (n/N):			
<400,000 IU/ml (n=52)	100 (24/24)	96.4 (27/28)	*p*=1.000[d]
≥400,000 IU/ml (n=35)	100 (18/18)	76.5 (13/17)	*p*=0.045
Genotype 2/3			
Yu *et al*., 2007[55]	**PEG α-2a + RBV 24 wks, n=100**	**PEG α-2a + RBV 16 wks, n=50**	**p-value**
SVR by RVR, % (n/N):			
RVR	98 (85/87)	100 (43/43)	*p*=1
no RVR	77 (10/13)	57 (4/7)	*p*=0.610
von Wagner *et al*. [56]	**PEG α-2a + RBV 24 wks, RVR n=71[e]**	**PEG α-2a + RBV 16 wks, RVR n=71[e]**	**p-value**
SVR by RVR and baseline viral load, % (n/N):			
≤800,000 IU/ml (n=66)	87 (27/31)	94 (33/35)	*p*=not reported
>800,000 IU/ml (n=75)	75 (30/40)	69 (24/35)	*p*=not reported

[a]for sub-group of patients who first became HCV RNA negative at week 4. Results are also presented in the trial publication for a sub-group of patients who became HCV RNA negative between weeks 1-3. Therefore the results presented in the table are not for all patients 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 48wks (n=208) based on time when HCV RNA first became undetectable (corresponding to 3, 4, 5, 6, 7 or 8 wks respectively) – results for the 24 wk subset only (n=28) are presented here;[c]variable treatment arm was 24, 48 or 72wks (n=459) based on time when HCV RNA first became undetectable – results for the 24 wk

subset only (n=123) are presented here; [d]difference -3.6% (95% CI -14.3% to -0.6%).[e] randomised at wk 8 according to RVR at wk 4 – patients not achieving RVR not reported here;

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 sub-group of patients who achieved an RVR and had LVL at baseline, the threshold used was ≤ or >800,000 IU/ml which differs from the threshold of <600,000 IU/ml specified in the SPC for the study drug, peginterferon α-2b.[43] For this reason we do not present the results for this sub-group, but instead present the SVRs for the sub-group who achieved an RVR irrespective of their baseline viral load. Since 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 genotype 2/3. Rates were similar in five trials, ranging from 83% to 100% for standard treatment duration compared to 84% to 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] where 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 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 sub-groups were small and none of the trials were powered for this sub-group analysis. In the trial by Mangia and colleagues[52] particularly, only 10% of patients had an RVR and LVL.

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

4.1.3.2 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 to those who received shortened courses, for both genotype 1 and genotype 2/3.

Table 4 Rapid virological response

Study details	Group 1	Group 2	*p*-value
Genotype 1			
Berg *et al*.[59]	**PEG α-2b + RBV 48 weeks, n=225**	**PEG α-2b + RBV 24 weeks, n=28[a]**	
% with response (n/N)[b] RVR	8.4 (19/225)[c] 35 (78/225)[d]	13.5 (28/208)[c] 37 (76/208)[d]	*p*=not reported
Mangia *et al*.[52]	**PEG α-2a or α-2b + RBV 48 wks, n=237**	**PEG α-2a or α-2b + RBV 24 wks, n=123[e]**	
% with response (n/N) RVR	26.2 (62/237)	26.8 (123/459)[f] 100 (123/123)[g]	*p*=0.90
Liu *et al.*[53]	**PEG α-2a + RBV 48 wks, n=154**	**PEG α-2a + RBV 24 wks, n=154**	
% with response (n) RVR	63 (97)	68 (104)	*p*=0.47
Yu *et al*., 2008[54]	**PEG α-2a + RBV 48 wks, n=100**	**PEG α-2a + RBV 24 wk, n=100**	
% with response RVR	42	45	*p*=not reported
Genotype 2/3			
Yu *et al*., 2007[55]	**PEG α-2a + RBV 24 wks, n=100**	**PEG α-2a + RBV 16 wks, n=50**	
% with response (n/N) RVR	87 (87/100)	86 (43/50)	*p*=not reported

von Wagner *et al*. [56]	**PEG α-2a + RBV 24 wks, RVR n=71[h]**	**PEG α-2a + RBV 16 wks, RVR n=71[h]**	**PEG α-2a + RBV 24 wks, no RVR, n=11[h]**	
% with response (n/N) RVR	100	100	0	*p*=not reported

ns = not significant; [a]variable treatment arm was 18, 24, 30, 36, 42 or 48wks (n=208) based on time when HCV RNA first became undetectable (corresponding to 3, 4, 5, 6, 7 or 8 wks respectively) – results for the 24 wk subset only (n=28) are presented here; [b]percentages calculated by reviewer from numbers presented in trial publication; [c]rates are for the sub-group of patients who became HCV RNA negative at week 4 only (not including those who became first negative between weeks 1-3); [d]we have combined the total number

of patients first becoming HCV RNA negative between weeks 1 to 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 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 wk 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 wk 8 according to RVR at wk 4.

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% to 68% of patients achieved an RVR, although in the sub-set of patients treated for 24 weeks in the Mangia and colleagues' trial,[52] all the patients achieved an RVR as per the study design (see section 4.1.2). The rates in this trial were lower than in the other five trials 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 (2007),[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% due 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 α-2a compared to peginterferon α-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 end of treatment 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 sub-group 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.

4.1.3.3 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 (2008)[54] was the only included trial to report the relapse rate in the sub-group of patients with an RVR and LVL (Table 5). In this sub-group, rates of relapse were low and were not statistically significantly different between treatment arms (3.6% vs 0 for 24 weeks vs 48 weeks respectively, difference 3.6% (95% 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).

Table 5 Relapse rate

Study details	Group 1	Group 2	*p*-value
Genotype 1			
Yu *et al*., 2008[54]	**PEG α-2a + RBV 48 wks, n=100**	**PEG α-2a + RBV 24 wk, n=100**	
Relapse rate by RVR and baseline viral load, % (n/N):			
<400,000 IU/ml (n=52)	0 (0/24)	3.6 (1/28)	*p*=1.000[a]
≥400,000 IU/ml (n=35)	0 (0/18)	23.5 (4/17)	*p*=0.045

[a]difference 3.6% (95% CI -7.2% to 6.6%).

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 sub-group of patients of relevance to this systematic review (i.e. those with both LVL and an RVR).

4.1.3.4 Biochemical response

Two RCTs reported biochemical response rate (normalization of ALT levels).[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 normalization rate compared to 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 sub-group 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 6 Biochemical response

Study details	Group 1	Group 2	*p*-value
Genotype 1			
Liu *et al*. [53]	**PEG α-2a + RBV 48 wks**	**PEG α-2a + RBV 24 wks**	
% with response (n)	72 (107)	51 (75)	*p*<0.001
Genotype 2/3			
von Wagner *et al*. [56]	**PEG α-2a + RBV 24 wks, RVR n=71**	**PEG α-2a + RBV 16 wks, RVR n=71**	
% with response	87	89	*p*=not reported

4.1.3.5 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 compared to 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 sub-group of patients with an RVR or RVR and LVL (Table 7).

Table 7 Histological response

Study details	**Group 1**	**Group 2**	***p*-value**
Genotype 1			
Liu *et al*. [53]	**PEG α-2a + RBV 48 wks**	**PEG α-2a + RBV 24 wks**	**p-value**
% with response (n)	78 (97)	59 (71)	*p*=0.001

4.1.3.6 Adverse events

Adverse events for the included studies are presented in Table 8. All the trials presented adverse events for treatment groups as a whole, not for the sub-group 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 (2008)[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 in genotype 2/3 patients,[56] 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.

For four trials,[54-56,59] the incidence of drug dose modifications for adverse events / lab abnormalities (classified by the studies as either peginterferon α-2a, RBV, peginterferon α-2a or

RBV, or peginterferon α-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 to 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, whilst in one trial,[53] 12 of the 15 events were considered to be treatment related (3/4 vs 9/11 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, dyspnea 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 were 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] whilst two trials [56,59] presented no statistical comparison between treatment groups. Liu and colleagues[53] found that bodyweight loss (weight reduction of >10% from baseline weight) was encountered less frequently in those receiving treatment for 24 weeks compared to 48 weeks (19% vs 30% respectively, p=0.03). In the trial by Yu and colleagues (2007),[55] the incidence of alopecia was significantly lower in the 16 week group compared to the 24 week group (20% vs 49% respectively, p=0.001).

Table 8 Adverse events

Reported adverse events % (n) of patients affected	Berg *et al*. [59] Genotype 1		Mangia *et al*. [52] Genotype 1		Liu *et al*.[53] Genotype 1		Yu *et al*., 2008[54] Genotype 1		Yu *et al*., 2007[55] Genotype 2		von Wagner *et al*. Genotype 2/3	
	PEG α-2b + RBV 48 wks, (n=225)	PEG α-2b + RBV Variable* (n=208)	PEG α-2a or α-2b + RBV 48 wks (n=237)	PEG α-2a or α-2b + RBV Variable* (n=459)	PEG α-2a + RBV 48 wks (n=154)	PEG α-2a + RBV 24 wks (n=154)	PEG α-2a + RBV 48 wks (n=100)	PEG α-2a + RBV 24 wk (n=100)	PEG α-2a + RBV 24 wks (n=100)	PEG α-2a + RBV 16 wks (n=50)	PEG α-2a + RBV 24 wks, RVR (n=71)[§]	PEG + RB 16 w RVR (n=7
Dose discontinuation	3 (7)	2 (4)	10 (24)	13 (59)	9 (14)	4 (6)	10 (10)	3 (3)[a]	1 (1)	0	8 (6)	1 (1)
adverse event			7 (16)	7 (30)			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[†] 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)[‡]	
Deaths, n	NR	NR	NR	NR	1	0	NR	NR	NR	NR	NR	NR

NR, not reported; *results presented for all patients in the variable treatment arm as adverse events not reported for 24 wk subset only; [§]randomised at wk 8 according to RVR at wk 4 – patients not achieving RVR not reported here; [†]dose modification or transient interruption for Yu 2008[54] and von Wagner[56] trials; [‡]7 out of whole study population (n=153); [a]p=0.045.

4.1.3.7 Clinical-effectiveness: summary

- All six included RCTs were in patients eligible for shortened treatment duration. No RCTs comparing peginterferon alfa with or without ribavirin compared to BSC were identified for the HCV/HIV co-infection nor re-treatment patient groups.
- In the sub-group 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 genotype 2/3. This infers that this patient group can receive shortened courses of peginterferon combination therapy without compromising SVR rates.
- For both genotype 1 and genotype 2/3 patients, there were no statistically significant differences in rates of RVR between treatment groups who received the standard duration of treatment compared to 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 sub-group 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 compared to 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 sub-group 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 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 were powered for sub-group analysis and therefore the results should be interpreted with caution.

4.1.4 Ongoing studies

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

NCT 00532701. Peginterferon α-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 (*eligibility criteria includes serum HCV RNA with dynamic range 25 ~ 391,000,000 IU/ml*). Study type: Phase IV, open-label, parallel RCT. Sample size: 700. Start date: June 2006. Estimated study completion date: June 2009. Status: the study is currently recruiting participants. Funding: National Taiwan University Hospital. Funding amount: not stated.

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; or
- who are co-infected with HIV, compared to 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 health related quality of life (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).

5.1 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 sub-groups outlined above (see Section 3 for methods). The details of the search strategy are documented in Appendix 2.

5.1.1 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 below.

Table 9 Study characteristics of the included economic evaluations

	Kuehne and colleagues [64]	**Campos and colleagues [65]**
Publication year	2002	2007
Country	United States	United States
Study type	Cost-utility analysis (CUA) model	Cost-effectiveness analysis (CEA) model
Study population	A cohort of HCV/HIV co-infected individuals	A treatment eligible urban cohort, co-infected with HCV/HIV
Interventions	a) Interferon alfa (48 weeks) b) Interferon alfa and ribavirin (24 and 48 weeks) c) Peginterferon alfa (48 weeks) d) Peginterferon alfa and ribavirin (48 weeks) e) No treatment	a) Peginterferon α-2a and ribavirin (48 weeks) b) Interferon α-2a and ribavirin (48 weeks) c) Peginterferon α-2a (48 weeks) d) No treatment
Treatment effect modelled	Patients were assumed to have: a) No treatment response: received no clinical benefit and were subject to their annual pre-treatment risk of HCV-related liver disease progression b) Partial but non-sustained response: did not progress in their HCV–related liver disease during treatment but were subject to pre-treatment risks of liver disease once treatment was stopped c) 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 peginterferon α-2a and ribavirin) of 40%, based on one trial[66]
Currency base	US$	2004, US$

The two included studies evaluated treatment of HCV/HIV co-infected cohorts. No economic evaluations were identified in re-treated cohorts, nor in patients eligible for shortened courses of treatment. Both included studies were conducted in the US and each of the studies compared peginterferon alfa and ribavirin with peginterferon alfa monotherapy, combined non-peginterferon alfa and ribavirin and with no treatment. An additional interferon alfa monotherapy arm was included in the Kuehne and colleagues study.[64] Kuehne and colleagues (2002)[64] present a cost-utility analysis, while in the more recent Campos and colleagues paper (2007)[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]

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.

Table 10 Methodological quality of the included economic evaluations

	Kuehne and colleagues[64]	**Campos and colleagues[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?	Not reported	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

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 was conducted prior to the publication of trials of anti-viral 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] employed an effectiveness measure from a large RCT of co-infected patients: the APRICOT (AIDS Pegasys Ribavirin International Co-infection Trial) 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 employ 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] of 16.9% vs. 14.9% respectively. Campos and colleagues' model 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] vs 16% in Campos and colleagues,[65] over the same follow up period.

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 at 3%; no discount rate is reported in the Kuehne and colleagues paper. 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 quality of life, 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 is 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 employed 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 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 employed 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.

Table 11 SVR probabilities in the two included economic evaluations[64,65]

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

Kuehne and colleagues' annual SVR probabilities are considerably higher than those reported by Campos and colleagues 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 reported 75% (61-85%) compared with Campos and colleagues 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% in Kuehne and colleagues vs. 31% in Campos and colleagues' for genotype non-1. In patients receiving peginterferon combined with ribavirin these probabilities were again higher in the Kuehne study: in genotype 1 Kuehne and colleagues reported 42% (34-45%) vs. 29% in the Campos study, and in genotype non-1 they were 79% vs. 58% respectively. In all treatment strategies and genotypes, with the exception of

genotype 1 and peginterferon alfa monotherapy, Kuehne and colleagues 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 (QALMs) and quality adjusted life years (QALYs). The authors stated that the quality weights for HCV-specific health states were derived from published studies using the visual analog 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 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 α-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 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).

5.1.1.1 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.

5.1.2 Assessment of cost-effectiveness

The base case results reported by Kuehne and colleagues[64] are presented in Table 12 and Table 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, whilst Kuehne and colleagues[64] have reported results by CD4 cell count (350 cells/µL and 200 cells/µL), by mild or moderate disease and by genotype 1 or non-1. Both studies report the incremental cost by YLS, and Kuehne and colleagues additionally present incremental costs per QALY for each subgroup.[64]

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

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

Interferon = non-peginterferon monotherapy; Int + RBV = non-peginterferon and ribavirin combination therapy; Peg Int = peginterferon monotherapy; Peg Int + 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 13 Base case results for genotype non-1 co-infected patients (Kuehne and colleagues[64])

Patient group	Treatment type	$/ YLS	$/QALY
Co-infected patients with CD4 cell counts of 350 cells/µL and mild chronic HCV	No treatment	. . .	. . .
	Interferon 48 wks	Dominated [a]	Dominated [a]
	Int + RIB 24 wks	37,400	11,900
	Int + RIB 48 wks	347,000	112,100
	Peg Int 48 wks	Dominated [b]	Dominated [b]
	Peg Int + RIB 48 wks	894,000	300,800
Co-infected patients with CD4 cell counts of 200 cells/µL and mild chronic HCV	No treatment	. . .	. . .
	Interferon 48 wks	Dominated [a]	Dominated [a]
	Int + RIB 24 wks	541,300	104,400
	Int + RIB 48 wks	3,865,600	1,088,500
	Peg Int 48 wks	Dominated [b]	Dominated [b]
	Peg Int + RIB 48 wks	11,827,300	4,000,000
Co-infected patients with CD4 cell counts of 350 cells/ µL and moderate chronic HCV	No treatment	. . .	. . .
	Interferon 48 wks	4,700	2,900
	Int + RIB 24 wks	Dominated [b]	Dominated [b]
	Int + RIB 48 wks	63,500	38,800
	Peg Int 48 wks	Dominated [b]	Dominated [b]
	Peg Int + RIB 48 wks	169,700	105,300
Co-infected patients with CD4 cell counts of 200 cells/ µL and moderate chronic HCV	No treatment	. . .	. . .
	Interferon 48 wks	Dominated [a]	Dominated [a]
	Int + RIB 24 wks	67,900	29,800
	Int + RIB 48 wks	561,200	265,100
	Peg Int 48 wks	Dominated [b]	Dominated [b]
	Peg Int + RIB 48 wks	1,558,800	771,200

Interferon = non-peginterferon monotherapy; Int + RBV = non-peginterferon and ribavirin combination therapy; Peg Int = peginterferon monotherapy; Peg Int + 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 (Campos and colleagues[65])

Patient group	Treatment strategy	Incremental cost per YLS ($)
Men, genotype 1	Peginterferon and ribavirin	73,000
Men, genotype non-1	Peginterferon and ribavirin	39,700
Women, genotype 1	Peginterferon and ribavirin	70,000
Women, genotype non-1	Peginterferon and ribavirin	39,300

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.

In Kuehne and colleagues' study,[64] both peginterferon alfa monotherapy and peginterferon alfa and 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 and ribavirin, and interferon and ribavirin dominated, while the latter was the most cost-effective at $11,600 vs. $40,000 for peginterferon in combination, per QALY gained.

In the base case analysis for genotype non-1 patients, again peginterferon alfa and 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 cells/μL and 200 cells/μL, the lowest cost per QALY gained came from the 24 week course of interferon and ribavirin at $11,900 and $104,400 respectively. In both cases the peginterferon and ribavirin (48 weeks) was the least cost-effective of the dominating strategies at $300,800 in patients with 350 cells/μL and $4,000,000 in patients with 200 cells/μL.

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 $2,900 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 sub-group 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 half 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: $73,000 (men) vs. $70,000 (women) in genotype 1, and $39,700 (men) vs. $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]

5.1.2.1 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 and ribavirin and disease progression, Campos and colleagues reported that cost-effectiveness ratios were less than $50,000 per YLS regardless of fibrosis where treatment efficacy exceeded 50%. This is higher than the base case treatment efficacy of 40%. Where treatment efficacy was below 25%, cost-effectiveness ratios were less than $100,000 across the range of relative risks (RR), although these are described as having had 'slightly more influence' (page 277). No further details of how, or the degree to which, the RR is influential are reported. Kuehne and colleagues reported that in mild HCV and peginterferon and 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 greater than 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 early virological response - $59,300 per YLS for men in genotype 1 vs. $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 due to HIV, fibrosis progression rates and treatment efficacies in non-cirrhotic patients, and as being 'moderately' sensitive to drug costs. None of these were reported in detail across the patient subgroups or intervention strategies. Where no discount rate was applied this resulted in an ICER 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 between $56,300 and $88,000 per YLS respectively. The variation in death rate due to HIV was illustrated by an example of the excess mortality being reduced by 97% reducing the ICER to $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 and 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 below $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 below $100,000 per YLS. The authors state this was 'slightly more' sensitive to fibrosis progression.

Kuehne and colleagues[64] performed a number of one-way sensitivity analyses in patients receiving interferon alfa and ribavirin and peginterferon and 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 and ribavirin compared with interferon alfa and ribavirin for 48 weeks. Minor adverse events are reported as having little impact on the ICERs, whilst major toxicity in 20% of patients receiving 48 weeks of peginterferon combination therapy increased this ICER from $40,000 to $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 $40,600 to $69,000 per QALY.

5.1.3 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, employing 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 US and therefore both the setting and costs are unlikely to be generalisable to the UK NHS.
- There are notable differences in the SVR probabilities employed by the two included studies. This is likely to be due to SVRs in the study by Kuehne and colleagues 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, 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 relative risks were derived.
- In the Kuehne and colleagues' study[64] a clear pattern does not emerge over the reported sub-groups. While peginterferon and ribavirin is a dominant strategy in each sub-group, it is not the most cost-effective strategy in any of these groups.
- Campos and colleagues[65] concluded that peginterferon alfa and ribavirin is the dominating strategy in all patient subgroups reported. In contrast Kuehne and colleagues[64] reported varied results across their sub-groups but in each, peginterferon and ribavirin combination therapy was the least cost-effective of the dominating strategies.
- These results should be viewed with caution due to the mixed methodological quality of the included studies.

5.2 Review of manufacturers' submissions

5.2.1 Roche submission to NICE: cost-effectiveness analysis

Overview

The Roche submission to NICE in support of peginterferon α-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 α-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 for NICE TA106.[17] 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 a 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 α-2a of 72 weeks). The model has five health states indicating progressive liver disease (HCV, compensated cirrhosis, decompensated cirrhosis,

hepatocellular carcinoma 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 later, 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 (discussed later).

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, 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 75kg – again this has no impact on the patient response to treatment, but has an impact on the cost of treatment, since 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.{10654} Age-specific utility values (reported for a general population survey using the EQ-5D[83] and valued using a UK general population tariff[84]) were applied only for 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

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

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	1,000/1,200[a]	84.15/ 100.98	72
	Genotype non-1	800	67.32	48
Re-treatment of relapsed patients	Genotype 1	1,000/1,200[a]	84.15/ 100.98	48
	Genotype non-1	800	67.32	48
Shortened duration of treatment	Genotype 1	1,000/1,200[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

[a]Weight-based ribavirin dosage for genotype 1 patients – 1,000 mg per day for body weight <75kg and 1,200 mg per day for body weight ≥75kg; [b]shortened duration of treatment – first value is standard duration, second number is shortened duration. Dosing is constant across duration of treatment.

Resource use for patient monitoring associated with peginterferon α-2a and ribavirin combination therapy and surveillance of patients following treatment cessation was estimated using management protocols, developed using expert opinion for our previous report for NICE appraisal TA106.[17] The original costing protocols were slightly modified (to include quantitative, rather than qualitative, HCV viral load at key assessment stages) and were

inflated to 2007/08 prices using the Hospital and Community Health Services (HCHS) Pay and Prices Index[85] (see Table 16).

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

	Cost (£)
On-treatment monitoring	
12 weeks	568
16 weeks	600
24 weeks	795
48 weeks	1,473
72 weeks	1,711
Post-treatment surveillance	
Non-responders	102
Responders (SVR)	167

Health state costs in the model are based on values adopted in our previous assessment,[17] inflated from 2003/4 to 2007/08 prices using the HCHS Pay and Prices Index[85] (see Table 17).

Table 17 Health state costs applied in the Roche model

Health state	**Health state cost (£)**
Moderate Chronic Hepatitis C	843
Compensated Cirrhosis	1,338
Decompensated Cirrhosis	10,725
Hepatocellular Carcinoma	9,557
Liver transplantation, 1st year	43,263
Liver transplantation, subsequent years	1,628

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 α-2a combination therapy and each comparator modelled separately, as well as an incremental analysis (these are summarised below in Table 18). Scatterplots showing the cost-effectiveness plane (incremental cost and incremental QALYs for peginterferon α-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.

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	3,334
		PEG 2a+RBV[a]	29,224	11.69	
	Non-1	No treatment	27,114	11.06	809
		PEG 2a+RBV[b]	27,942	12.08	
Relapsed on previous treatment	All	No treatment	27,114	11.06	Dominant
		PEG 2a+RBV	21,199	13.74	
Shortened treatment duration for patients with LVL and RVR	1 + 4	PEG 2a+RBV 48 wks	13,387	15.78	15,472
		PEG 2a+RBV 24 wks	8,866	15.49	
	2 + 3	PEG 2a+RBV 24 wks	8,053	15.64	2,719
		PEG 2a+RBV 16 wks	7,391	15.39	
HCV/HIV co-infected patients	All	IFN 2a+RBV	32,431	11.62	Dominant
		PEG 2a+RBV	28,786	12.99	

[a]72 weeks treatment for patients showing an EVR, 12 weeks treatment for patients not showing an EVR; [b]48 weeks treatment for patients showing an EVR, 12 weeks treatment for patients not showing an EVR.

The MS states that peginterferon α-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 α-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 no-genotype 1 patient sub-groups);
- treatment for patients who relapsed on previous peginterferon alfa treatment and for HCV/HIV co-infected patients were 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, while 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 1/4 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 genotype 1 + 4 total cost is reduced by £4,500 and total QALYs are 0.29 lower while for genotype 2 + 3 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) on page 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, that is where the value of incremental benefits exceeds the incremental costs. 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:

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 (see Table 19) the incremental net monetary benefit for shortened duration of treatment is positive for genotype 2/3 only at comparatively low threshold values (below the ICER value of £2,719). 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).

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

	ΔC	**ΔE**	**0**	**£10,000**	**£20,000**	**£30,000**
Genotype 1 + 4	-£4,521	-0.29	4,521	1,599	-1,323	-4,245
Genotype 2 + 3	-£662	-0.24	662	-1,773	-4,208	-6,643

Outline appraisal of the cost-effectiveness analysis undertaken

Table 20 NICE 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	✓

[a]Comparator for HCV/HIV co-infected patients is IFN α2a + 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 Hep 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 over-estimation of the utility gain from treatment response.

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 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 doesn't present a review of published economic evaluations or discuss alternative approaches to modelling the cost-effectiveness of anti-viral 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, hepatocellular carcinoma and liver transplantation) are commonly accepted as distinct stages of progressive liver disease which can be distinguished by their impact on quality of life, 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 doesn't report any evidence of approaches to establish the internal consistency of the model, nor 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 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. 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 anti-viral 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[87] for non-responders and Berg and colleagues[88] for patients who relapsed – see Appendix 3). The SVR for the no treatment group was assumed to be zero, since none of the trials were placebo controlled or contained BSC arms. As acknowledged in the MS, the SVR reported by Berg and colleagues[88] 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,[88] 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, 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 sub-group analyses of clinical trial subjects. For genotype 2 and

3 patients the sub-groups were taken from the trial reported by Shiffman and colleagues[89], and for genotype 1 and 4 sub-groups appear to have been taken from the trial reported by Hadziyannis and colleagues[90] (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 α-2a with peginterferon α-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[87] for non-responders and Berg and colleagues[88] 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 α-2a[42], see page 4 of SPC)

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" (page 216), but only gives 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 quality of life or utility data in the specific populations of patients included in their submission. As a result the model uses utility values from the UK Mild Hepatitis C Trial,{10654} 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 over-estimation 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.{10654} 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 over 75. In contrast the utility for patients achieving an SVR

from moderate HCV, using the UK Mild Hepatitis C Trial{10654} 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 2007/08 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 α-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 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 standard errors 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 states costs are reported by the UK Mild Hepatitis C Trial{10654} and could have been used to parameterise the distributions. Scatterplots of incremental cost and incremental QALYs are presented for all comparisons, while CEACs are only presented 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 to that estimated in the UK Mild Hepatitis C Trial. This cost is only applied 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 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 21 Additional analysis for patients eligible for shortened duration of treatment with peginterferon α-2a combination therapy

		Genotypes 1 + 4		Genotypes 2 + 3	
		Cost (£)	**Outcome**	**Cost (£)**	**Outcome**
Original	Standard	13,387	15.78	8,053	15.63
	Shortened	8,866	15.49	7,391	15.39
	ICER	15,472		2,719	
Do not use age-specific utility	Standard	13,387	14.16	8,053	14.07
	Shortened	8,866	13.97	7,391	13.91
	ICER	23,541		4,137	
Stage distribution	Standard	13,125	15.83	7,529	15.73

(50:50 mild and moderate)	Shortened	8,081	15.64	6,431	15.57
	ICER	26,146		6,830	
Stage distribution (33:35:32 mild:moderate:CC)	Standard	13,358	15.78	7,995	15.62
	Shortened	8,780	15.47	7,285	15.37
	ICER	15,071		2,805	
Add cost of original health state to Yr1 SVR	Standard	13,796	15.78	8,449	15.63
	Shortened	8,866	15.49	7,391	15.39
	ICER	16,872		4,347	
All together[a]	Standard	13,735	14.16	8,360	14.05
	Shortened	8,780	13.95	7,285	13.88
	ICER	24,334		6,336	

[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 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, while these analyses suggest the ICER for re-treating patients with peginterferon α-2a combination therapy may be higher than the manufacturer's base case, they do not substantially alter the conclusions from the analysis. In all the alternative scenarios, re-treatment of relapsing patients remains dominant.

Table 22 Additional analysis for non-responding patients and for relapsing patients treated with peginterferon α-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 2a	29,225	11.69	27,942	12.08	21,199	13.74
	ICER	3,334		809		PegIFN dominates	
Do not use age-specific utility	BSC	27,114	11.06	27,114	11.06	27,114	11.06
	PEG 2a	29,225	11.47	27,942	11.73	21,199	12.82
	ICER	5,073		1,232		PegIFN dominates	
Stage distribution (50:50 mild and moderate)	BSC	18,392	12.71	18,392	12.71	18,392	12.71
	PEG 2a	21,637	13.13	21,052	13.39	17,274	14.48
	ICER	7,763		3,939		PegIFN dominates	
Stage distribution (33:35:32 mild:moderate:CC)	BSC	26,153	10.86	26,153	10.86	26,153	10.86
	PEG 2a	28,389	11.52	27,183	11.93	20,766	13.65
	ICER	3,397		968		PegIFN dominates	
Add cost of original health state to Yr1	BSC	27,114	11.06	27,114	11.06	27,114	11.06
	PEG 2a	29,280	11.69	28,030	12.08	21,431	13.74

SVR	ICER	3,421		896		PegIFN dominates	
All together[a]	BSC	26,153	10.86	26,153	10.86	26,153	10.86
	PEG 2a	28,440	11.31	27,265	11.58	20,980	12.73
	ICER	5,182		1,559		PegIFN dominates	

[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 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 α-2a combination therapy may be higher than the manufacturer's base case, they do not substantially alter the conclusions from the analysis.

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

		Cost (£)	Outcome
Original	BSC	27,022	11.03
	PEG 2a	28,786	12.99
	IFN 2a	32,431	11.62
	ICER	903	
Do not use age-specific utility	BSC	27,022	11.03
	PEG 2a	28,786	12.32
	IFN 2a	32,431	11.42
	ICER	1,372	
Stage distribution (50:50 mild and moderate)	BSC	18,320	12.68
	PEG 2a	23,565	13.97
	IFN 2a	24,773	13.07
	ICER	4,050	
Stage distribution (33:35:32 mild:moderate:CC)	BSC	26,080	10.84
	PEG 2a	28,221	12.87
	IFN 2a	31,602	11.45
	ICER	1,054	
Add cost of original health state to Yr1 SVR	BSC	27,022	11.03
	PEG 2a	28,955	12.99
	IFN 2a	32,431	11.62
	ICER	989	
All together	BSC	26,080	10.84
	PEG 2a	28,377	12.20
	IFN 2a	31,602	11.25
	ICER	1,684	

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.

5.2.2 Schering-Plough submission to NICE: cost-effectiveness analysis

Overview

The Schering-Plough submission 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 previously been treated 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 (genotype 1 and 4 combined, or genotype 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 (genotype 1 and 4 combined, or genotype 2 and 3 combined). Costs and outcomes for these patients is 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 maybe due to peginterferon α-2b only being licensed for shorter treatment durations in genotype 1 (as opposed to genotypes 2, 3 or 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 α-2b combined with ribavirin compared with BSC.

The MS does not report whether a systematic search was undertaken for economic evaluations of peginterferon α-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 they emerge from the decision – either 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 quality of life data reported by the UK Mild Hepatitis C Trial{10654} 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 maybe 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 sub-groups 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, since peginterferon α-2b and ribavirin dosage is weight-related.

The health state utilities have been derived from the UK Mild Hepatitis C trial{10654}, and a study of the cost-effectiveness of liver transplantation.[91] 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,{10654}, at 24 or 48 weeks post-treatment or control. A linked observational study employed 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 employed 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 (due 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.{10654} 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 states costs. Health state costs include resource use associated with the management of progressive liver disease.

Drug usage for peginterferon α-2b was based on a dosage of 1.5 micrograms per kg per week and was assumed to be supplied in pre-filled pens. Since dosage of both peginterferon α-2b and ribavirin is weight-based (see Table 24) the MS needed to assume an average weight for each of the modelled patient populations. A mean weight of 80kg was applied in the base case

analysis for the re-treated group, and of 63kg in the HCV/HIV co-infected group. The values for the weight of the HCV/HIV co-infected group were taken from the Laguno 2009 study,[92] however the default value in the MS is reported as 68.29kg.

Table 24 Peginterferon α-2b and ribavirin, weight-based dosage

Body weight (kg)	Peginterferon α-2b		Ribavirin	
	Vial/pen strength (µg/ml)	Administer once weekly (ml)	Total daily dose (mg)	Number 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	1,000	5
76-85	120	0.5	1,000	5
86-105	150	0.5	1,200	6
>105	150	0.5	1,400	7

The drug acquisition costs for peginterferon α-2b and ribavirin adopted in the Schering-Plough submission (taken from the BNF, March 2009) are presented in Table 25 and Table 26 below. With an assumed body weight of 80kg for re-treated patients, and assuming a preference for pre-filled pens for peginterferon α-2b and tablets for ribavirin, the weekly treatment costs are £165.73 for peginterferon α-2b and £114.85 for ribavirin. The equivalent cost for the HCV/HIV co-infected patients is £118 for peginterferon α-2b and £91.88 for ribavirin.

Table 25 Peginterferon α-2b acquisition cost

µg/ bottle	Pack costs (powder for reconstitution)	Pack cost (pre-filled 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

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 out-patients consultations and investigations. These costs were all taken from the Mild Hepatitis C trial{10654}. 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 this, (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{10654}, 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 81kg and it is assumed that 85% of re-treated patients have genotypes 1/4 (the remainder with viral genotypes 2/3). This last assumption has an impact on outcome for the overall cohort of patients, since patients with viral genotype 1 and 4 have a lower probability of SVR than those with viral genotype of 2 or 3. For patients with HCV/HIV co-infection, the base case characteristics are based on the RCT by Laguno and colleagues[93] with a mean age of 40, 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 sub-groups, the MS does not discuss how relevant these characteristics maybe 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 – either 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 sub-groups were used to estimate response for each sub-group. The overall results for the cohort were then calculated as weighted totals (based on the proportion of the total cohort in each sub-group). The model results are also presented as an average cost and average QALYs per patient for the cohort including all genotypes and for sub-groups of genotypes 1+4 and of genotypes 2+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 maybe 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 for re-treatment of patients who did not respond or relapsed following previous interferon therapy and for HCV/HIV co-infected patients. Scatterplots showing the cost-effectiveness plane (incremental cost and incremental QALYs for peginterferon α-2b combination therapy) and CEACs are presented in a separate section of the MS reporting the results of the PSA.

Table 27 Base case results from Schering-Plough economic evaluation

Patient group	Genotype	Treatment	Cost (£)	QALYs	ICER (£ per QALY gained)
Non-responders / relapsers	1 + 4	No treatment	22,130	9.97	7,177
		PEG 2b+RBV	27,125	10.67	
	2 + 3	No treatment	22,130	9.97	783
		PEG 2b+RBV	24,301	12.75	
	All	No treatment	22,130	9.97	4,387
		PEG 2b+RBV	26,666	11.01	
HCV/HIV co-infection	1 + 4	No treatment	24,494	10.90	1,637
		PEG 2b+RBV	27,790	12.91	
	2 + 3	No treatment	24,494	10.90	403
		PEG 2b+RBV	25,645	13.75	
	All	No treatment	24,494	10.90	1,077
		PEG 2b+RBV	26,997	13.22	

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 decribed 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 sub-groups is presented in Table 28 and shows that previous non-responders have a lower QALY gain (and higher incremental cost) than previous treatment failures and relapsing patients.

Table 28 Schering-Plough sub-group 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	2,048
	PEG 2b+RBV	25,996	11.86	
Previous non-responders	No treatment	22,130	9.97	7,581
	PEG 2b+RBV	27,009	10.62	
Prior treatment failures	No treatment	22,130	9.97	3,013
	PEG 2b+RBV	26,157	11.31	

The MS states that peginterferon α-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 deterministic sensitivity analyses (where ICERs remained below £20,000 per QALY gained in the scenarios tested) and from probabilistic sensitivity analyses where the probability for peginterferon α-2b being cost-effective, compared with no active treatment, for re-treating patients 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 α-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

Table 29 NICE 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	✓

[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.{10654} The states representing more advanced liver disease in the model (compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and liver transplantation) are commonly accepted as distinct stages of progressive liver disease. These can be distinguished by their impact on quality of life, 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, while lower than for non-responding patients, is not completely eradicated. Since patients can enter the model in the compensated cirrhosis state (and receive treatment) excluding a transition from the SVR state (for patient 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 quality of life data reported by the UK Mild Hepatitis C Trial{10654} 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 maybe 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 quality of life 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 anti-viral treatment for chronic HCV.

The MS doesn't report any evidence of approaches to establish the internal consistency of the model, nor 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[94] which is an open-label, single-arm study. The SVR for best supportive care was assumed to be zero for patients with moderate chrnic 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 best supportive care 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,[94] 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[93] which recruited treatment naïve (naïve 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.[94]

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{10654}, 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{10654}, 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 is no published data for patients' quality of life whilst receiving peginterferon alfa. The drug costs were taken from the SPC. The Mild Hepatitis C trial{10654} was used to inform further costs: those taken into account included liver biopsy to assess eligibility for treatment, regular outpatients 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[94] and Laguno and colleagues 2004.[93] The transitions between health states came again from the Mild Hepatitis C trial{10654}, 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 manafacturers' own submission. For example, on page 16 the authors stated that key predictors of SVR included fibrosis level and on page 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: the re-treatment group is presented as non-responders and relapsed patients, and a further scenario where 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 confidence intervals from the included studies. The ICER in this group then changed from £4,387 in the base case analysis to £4,842 where EVR proportion was 'low'

and to £4,003 where this was 'high'. The SVR was similarly varied, and the ICER changed to £5,227 in the 'low value' group and to £3,615' in the 'high value' group.

The peginterferon α-2b arm of the Scotto and colleagues[95] 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 £2,520 in the genotype 2 and 3 group and £10,742 for all patients. The manufacturers state that this is due to the re-treated patients in this study being previous non-responders.

ICERs 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 confidence intervals reported in the included study. The base case ICER was £1,077. In the 'low value' group this increased to £4,065 per QALY, and in the 'high value' group, peginterferon α-2b was dominant. When the EVR and SVR values from the more recent Laguno and colleagues 2009 RCT[92] were applied, the manufacturers report ICERs of £6,140 per QALY in genotypes 1 and 4, £422 per QALY for genotypes 2 and 3 and £2,311 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 decrease from 33% to 27%, in the case of moderate disease this proportion decreased from 33% to 31%, and in the case of compensated cirrhosis this proportion increased from 33% to 42%. This variation is quite small, and had the effect of decreasing the ICER to £3,596 per QALY from £4,387 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 £7,176 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 £1,637 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 £4,387. For the 'previous relapser' group alone it was £2,048 and for 'previous non-responders' alone in

this scenario it was £7,581 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 £1,265 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 (for example, 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 which lists the parameters included in the PSA, their mean value, standard error 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 sub-groups (genotype 1+4 and genotype 2+3). Cost-effectiveness scatterplots 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-topay 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 under-estimate the SVR in each analysis, as a result of applying an unnecessary adjustment for treatment discontinuation, but appears to over-estimate 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). Since the original SVR rate of 38% was based on the observed data reported in the RCT by Laguno and colleagues,[93] 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 doesn't 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,[96] 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 – Table 31 and Table 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

200mg tablet of ribavarin of approximately £3.28. However the figures used in the MS are the daily, not weekly cost.

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 only applying 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 stage F2, F3 and F4 (derived using data reported in the MS for the EPIC study) were used to examine the effect, on the cost effectiveness results, of reducing the SVR for cirrhotic patients. This is labelled in the tables as "Adjust SVR for disease stage".

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	1,637		403		1,077	
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	2,511		613		1,645	
Correct ribavirin 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	3,434		1,671		2,633	
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	1,992		649		1,382	
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	2,541		230		1,488	

[a]remove adjustment to SVR for discontinuation, differentiate SVR sccording to patients' stage of disease at baseline, correct error in ribavirin cost, apply SVR cost for one year only, and adjust SVR for disease stage (poorer response for cirrhotic patients)

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 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 α-2b combination therapy may be higher than in the manufacturer's base case, they do not substantially alter the conclusions from the analysis.

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	7,177		783		4,387	
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	6,463		535		3,881	
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		1,232		7,006	
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		2,195		6,785	
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	6,099		-251		3,329	
Adjust SVR for	BSC	22,130	9.97	22,130	9.97	22,130	9.97

disease stage	PEG	27,301	10.61	24,975	12.53	26,923	10.92
	ICER	8,102		1,114		5,047	
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		1,781		9,027	

5.2.3 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{10654} and Fattovich and colleagues.[97] The principle 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 by Bennett and colleagues[98] and cancer mortality statistics;[99]
- 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 tables included in the main submission document. This discrepancy is not explained in the submission or the electronic model.

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

Health State		Roche	Schering-Plough		SHTAC (2007) [17]	
From	To					
SVR	SVR	#	#		#	
	Mortality: Liver disease All cause	0 Age/sex-specific	0 Age/sex-specific		0 Age/sex-specific	
HCV	SVR	See Table 33	See Table 33			
	HCV	#	#	0	#	0
			0.025	#	0.025	#

	CC	0.037	0	0.037	0	0.037
	HCC	0	0	0.001	0	0
	Mortality: Liver disease All cause	0 Age/sex-specific	0 Age/sex-specific		0 Age/sex-specific	
CC	SVR	0	See Table 33			
	CC	#	#		#	
	DC	0.039	0.039		0.039	
	HCC	0.014	0.01441		0.014	
	Mortality: Liver disease All cause	0 Age/sex-specific	0.02 Age/sex-specific		0 Age/sex-specific	
DC	DC	#	#		0.039	
	HCC	0.014	0.01441		0.014	
	LT	0.02	0.022		0.02	
	Mortality: Liver disease All cause	0.129 0	0.130 Age/sex-specific		0.130 Age/sex-specific	
HCC	HCC	#	#		#	
	LT	0	0.02		0	
	Mortality: Liver disease All cause	0.427 0	0.560 Age/sex-specific		0.43 Age/sex-specific	
LT	LT	#	#		#	
	Mortality: Liver disease All cause	0.210 0	0.150 Age/sex-specific		0.150 Age/sex-specific	
Post-LT	Post-LT	#	#		#	
	Mortality: Liver disease All cause	0.057 0	0.057 Age/sex-specific		0.057 Age/sex-specific	

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

Table 33 SVRs used in manufacturers' models

Patient group	Roche		Schering-Plough	
	G1	G1 non-1	G1 / G4	G2 / G3
Non-responders	13%	21%	48.65%	69.95%
Relapsed	55%			
Shortened duration	91%[a]	89%[b]		
HIV co-infected	40%		38%	53%

[a]vs 97% for 48 weeks; [b]vs 94% for 24 weeks; unless otherwise noted SVR in comparator group assumed to be 0%.

Table 34 and Table 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 already 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 34 Health state utility in manufacturers' models, compared with SHTAC 2007

Health State	Roche	Schering-Plough	SHTAC (2007) [17]
SVR	0.91 (<45) 0.85 (45-54) 0.80 (55-64) 0.78 (65-74) 0.73 (≥ 75)	0.82	0.82 (from Mild) 0.72 (from Mod) 0.60 (from CC)
HCV	0.66	0.77 (Mild) 0.66 (Mod)	0.77 (Mild) 0.66 (Mod)
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 indicates that, while 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{10654} 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 or 24 weeks following randomisation (adopted by Schering-Plough).

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

Health State	Roche	Schering-Plough[a]	SHTAC (2007)[b17]
Treatment-year utility	0.55	0.64 (Mild) 0.53 (Mod) 0.42 (CC)	0.66 (Mild) 0.55 (Mod) 0.44 (CC)

[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.{10654} 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).

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

- 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);
- source 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.{10654} Roche have inflated health state costs reported in our previous assessment (which had been inflated from 2002/3 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 over time.

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

Health State	Roche (2007/08)	Schering-Plough[a] (Year not stated)	SHTAC (2007) [17] (2003/04 prices)	SHTAC[c] (2007/08 prices)
SVR	0	311	267 (Mild)[b] 267 (Mod) 585.50 (CC)	311 311 684
HCV	843.38	166 (Mild) 862 (Mod)	142 (Mild) 738 (Mod)	166 862
CC	1,338.21	1,368	1,171	1,368
DC	10,725.12	10,965	9,385	10,964
HCC	9,557.18	9,770	8,363	9,770
LT	43,262.74	44,953	37,857	44,225
Post-LT	1,628.48	1,665	1,425	1,665

[a] inflated using HCHS (value and source not stated) from 2002/03 costs reported for UK Mild Hepatitis C Trial;{10654} [b]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 (costs is half of CC health state cost); [c]costs from the UK Mild Hepatitis C Trial, {10654} inflated to 2007/08 prices using HCHS Pay and Prices Index.[85]
CC, compensated cirrhosis; DC, decompensated cirrhosis; LT, liver transplant; Post-LT, post-liver transplant

5.3 Methods for SHTAC independent economic analysis

5.3.1 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 α-2a and peginterferon α-2b for the treatment of chronic HCV, compared to current practice, in sub-groups of adults who:

- were eligible for a shortened duration of treatment with peginterferon α-2a;
- had failed to show a sustained virological response on previous treatment with peginterferon α-2a or peginterferon α-2b;
- were co-infected with HCV/HIV.

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

5.3.2 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).

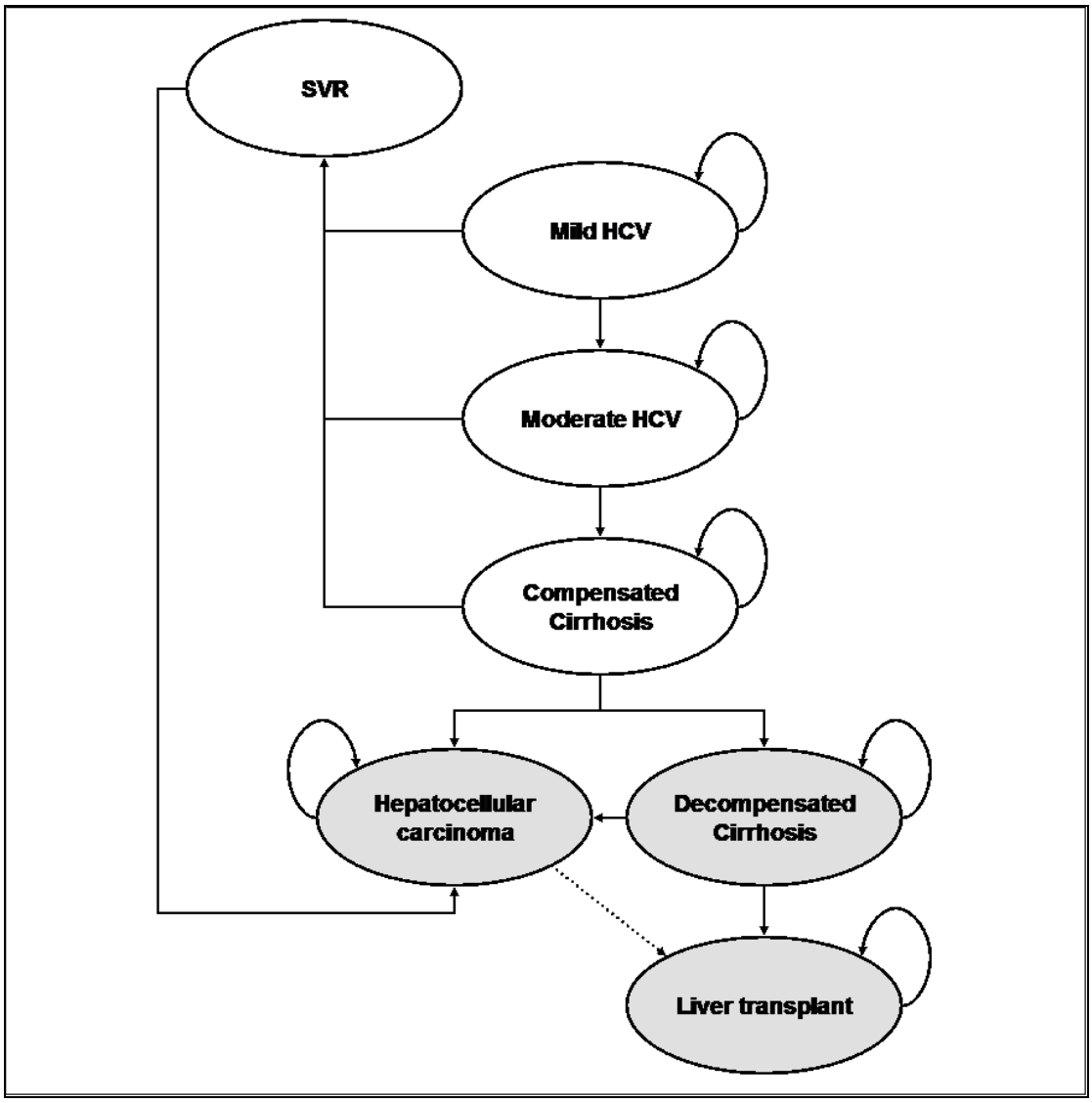
5.3.3 Model type and rationale for the model structure

The principal outcome of interest in the clinical trials systematically reviewed in Section 4 is the SVR, defined as undetectable HCV RNA in the serum for at least six 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.

Figure 2 State transition diagram for SHTAC economic model



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 (NB. our analysis does not consider the impact of onward 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.

The model has a lifetime horizon and a cycle length of one year, with a half-cycle correction applied. To take account of adverse effects of anti-viral treatment on HRQoL, health state utilities are reduced during the year in which treatment occurs.

5.3.4 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.[100,101] Patients eligible for shortened treatment durations and those with HCV/HIV co-infection have a mean age at entry to the model of 40, while re-treated patients have a mean age of 45. Seventy percent 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.[101] 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)

5.3.5 Data Sources

5.3.5.1 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]

Table 38 Transition probabilities for natural history model

Health state			
From	**To**	**Transition Probability**	**Source**
Mild disease	Mild disease	#	
	Moderate disease	0.025	Wright and colleagues,{10654} Grieve and colleagues[81]
Moderate disease	Moderate disease	#	
	Compensated cirrhosis	0.037	Wright and colleagues,{10654} Grieve and colleagues[81]
Compensated cirrhosis	Compensated cirrhosis	#	
	Decompensated cirrhosis	0.039	Fattovich and colleagues[97]
	Hepatocellular carcinoma	0.014	Fattovich and colleagues[97]
Decompensated cirrhosis	Decompensated cirrhosis	#	
	Hepatocellular carcinoma	0.014	Fattovich and colleagues[97]
	Liver transplant	0.020	Grieve and colleagues,[81] Siebert and colleagues[102]
	Death	0.130	Fattovich and colleagues[97]
Hepatocellular carcinoma	Hepatocellular carcinoma	#	
	Death	0.430	Fattovich and colleagues[97]
Liver Transplantation	Liver Transplantation	#	
	Death	Yr 1 = 0.150 Yr 2 = 0.057	Grieve and colleagues,[81] Bennett and colleagues[103]

#indicates that this is the default transition and is calculated as the complement of the other transition probabilities for each health state.

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{10654} and were based on a re-analysis of data from UK cross-sectional and longitudinal datasets. The remaining transition probabilities were taken from the literature on natural history and previous economic evaluations.[81,97,102,103] 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 sub-groups being considered. The studies used to estimate the effectiveness of treatment have typically reported SVRs for all patients in the relevant sub-group 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.

SVR estimates for patients receiving shortened courses of treatment are based on those used in our systematic review of clinical-effectiveness (see Section 4.1.3). SVR estimates for patients co-infected with HCV/HIV were based on those reported from two recent systematic reviews of anti-viral treatment in this patient group (further details are in Appendix 8). SVR estimates for patients re-treated following non-response to, or relapse from, a previous course of peginterferon α-2a were taken from the trial by Jensen and colleagues[87] supplemented with information from the Roche submission to NICE (see Appendix 8). SVRs for re-treatment with peginterferon α-2b were from the EPIC3 study,[94] as summarised in the Schering-Plough submission to NICE (see Appendix 8).

Table 39 Effectiveness input parameters used in analysis

Patient group/ treatment strategy	Intervention	Genotype	SVR		Withdrawal		Source
Shortened treatment duration	PEG α-2a + RBV	1	Standard duration 57/57 (100%) 24/24 (100%)	Shortened duration 69/73 (94.5%) 27/28 (96.4%)	Standard duration 14/154 (9.1%)[a] 8/100 (8.0%)[a]	Shortened duration 6/154 (3.1%)[a] 3/100 (3.0%)[a]	Liu *et al.*[53] Yu *et al.*, 2007[54]
		2 2 / 3	Standard duration 85/87 (97.7%) 27/31 (87.1%)	Shortened duration 43/43 (100%) 33/35 (94.3%)	Standard duration 1/100 (1.0%)[a] 1/71 (1.4%)[a]	Shortened duration 0/50 (0.0%)[a] 0/71 (0.0%)[a]	Yu *et al.*, 2008[55] von Wagner[56]
	PEG α-2b + RBV	1	Standard duration 8/19 (42.1%)	Shortened duration 16/28 (57.1%)	Standard duration 7/255 (2.7%)[a]	Shortened duration 4/208 (1.9%)[a]	Berg *et al.*[59]
Re-treated	PEG α-2a + RBV	1	18/142 (12.7%)		20/316 (6.3%)		Jensen *et al.*[87] Roche[104]
		non-1	6/29 (20.7%)				
	PEG α-2b + RBV	1+4	162/1121 (12.7%)		89/1341 (6.6%)		Schering-Plough[105]
		2+3	117/206 (20.7%)				
HCV/HIV co-infected	PEG α-2a + RBV	1+4	64/245 (26.1%)		91/606 (15.0%)[b] 99/606 (15.3%)[c]		Kim *et al.*,[51] Zhao *et al.*[50]
		2+3	59/95 (62.1%)				
	PEG α-2b + RBV	1+4	55/233 (23.6%)				
		2+3	71/152 (46.7%)				

[a] Withdrawal data applies to all patients in trial arm – not the sub-group included in the analysis of efficacy. Data for the relevant sub-group not reported.
[b] pooled data on patients discontinuing treatment due to adverse effects from meta analysis by Kim and colleagues[51]
[c] pooled data on patients discontinuing treatment due to adverse effects and laboratory abnormalities from meta analysis by Zhao and colleagues[51]

5.3.5.2 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 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.[17] These data are appropriate to the NICE reference case[68] for measuring and valuing health benefits, in that the quality of life measurements were undertaken using the EQ-5D in patients with chronic HCV recruited to the UK Mild HCV trial{10654}, 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.[91] The quality of life 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 treatment-naïve patients (as in the UK Mild HCV trial{10654}) may not be representative of utilities for patients who have been previously treated.

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
Decompensated cirrhosis	0.45
Hepatocellular carcinoma	0.45
Liver transplantation	0.45
Post-liver transplantation	0.67

5.3.5.3 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 2007/08 values (from 2003/04 prices) using the HCHS Pay and Prices Index[85] and are reported in Table 41.

Table 41 On-treatment monitoring costs by duration of treatment

On-treatment monitoring	Cost (£)
12 weeks	649
16 weeks	782
24 weeks	792
48 weeks	1,051
72 weeks	1,039

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 British National Formulary, number 58 (September 2009).[47]

Drug costs for peginterferon α-2a (Pegasys) were calculated for a dosage of 180 µg/0.5ml, 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 £3,046 for monotherapy and for 48 weeks is £6,092. Drug costs for ribavirin (Copegus), for dual therapy with peginterferon α-2a were calculated for a dosage of 800mg per day for genotype 2/3 and 1000-1200mg per day (depending on body weight, 1000mg for weight <75kg and 1200mg for weight >=75kg) for genotype 1. Patients co-infected with HCV and HIV also receive 800mg of ribavirin per day irrespective of genotype. A 168-tab packet of 200mg tablets costs £444.43. This corresponds to a weekly cost of £111 for genotype 1 (based on an average body weight of 79kg) and £74 for genotype 2/3. The total drug costs estimated for 24 weeks of dual therapy are £4,824 and are £11,425 for 48 weeks of dual therapy (or £9,647 for HCV/HIV co-infected patients having 48 weeks of dual therapy).

Drug costs for peginterferon α-2b (ViraferonPeg) were calculated for a patient weighing 79kg (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 £3,902 and for 48 weeks is £7,805. Dosage of ribavirin (Rebetol), used in dual therapy with peginterferon α-2b, is also weight-based (see Table 42). Drug costs for ribavirin, in combination with peginterferon α-2b, were calculated for a dosage of 1000mg per day, based on an average body weight of 79kg. A 168-tab packet of 200mg 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 α-2b plus ribavirin) of £5,540 for 24 weeks of treatment for genotype 2/3 patients and £11,081 for 48 weeks of treatment for genotype 1 patients.

Table 42 Weight-based dosing of ribavirin in combination with peginterferon α-2b

Body weight (kg)	Total daily dose of Rebetol (mg)
< 65 kg	800
65 to 85 kg	1,000
86 to 105 kg	1,200
> 105 kg	1,400

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.{10654} Costs for liver transplantation and post-liver transplantation were taken from a Department of Health funded study of the costs of liver transplantation.[106] Costs for 2002/03 have been updated to 2007/08 costs using the HCHS Pay and Prices Index.[85]

Table 43 Health state costs

Health state	Cost (£ per year) 2007/08 prices
SVR	311
Mild chronic HCV	142
Moderate chronic HCV	862
Compensated cirrhosis	1,368
Decompensated cirrhosis	10,964
Hepatocellular carcinoma	9,770
Liver transplantation	44,225
Post Liver transplantation	1,665

5.3.5.4 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.

5.3.5.5 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 in Section 5.3.4. 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 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.

5.3.5.6 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 in the natural history and treatment effects are reported in Table 38 and Table 39 and for health state costs in Table 43. Distributions are also assigned to the health state utilities described in Section 5.3.5.2 and these are sampled during the probabilistic analysis. Appendix 9 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.

5.4 Results of SHTAC independent economic analysis

5.4.1 Shortened treatment duration

Peginterferon α-2a

Costs and outcomes modelled for patients eligible for shortened duration of treatment with peginterferon α-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 α-2a and 2b within the same trial. As the two drugs are considered pharmacologically different we present cost-effetiveness

estimates for peginterferon α-2a based on RCTs of α-2a, and peginterferon α-2b based on RCTs of α-2b). The comparator in each of the analyses is the standard duration of peginterferon α-2a combination therapy (48 weeks for genotype 1 patients and 24 weeks for patients with genotype 2 or 3). The tables report total costs (anti-viral 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%.

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

RCT		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Liu *et al.*[53]	Standard (48 wks)	14,206	20.86	15.68	
	Shortened (24 wks)	9,399	20.76	15.54	
	Incremental	-4,807	-0.11	-0.14	34,510
Yu *et al.*, 2008[54]	Standard (48 wks)	14,206	20.86	15.68	
	Shortened (24 wks)	8,994	20.80	15.60	
	Incremental	-5,212	-0.07	-0.08	64,880

In both 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 sub-group 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 α-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 (to 94% in the trial by Liu and colleagues[53] and 96% in the trial by Yu and colleagues, 2008[54]) in SVR. Shorter duration of 24 weeks of treatment is associated with a reduction in total costs between £4,800 and £5,200. 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 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 quality of life impact of treatment-related adverse events estimated for the cohort of patients receiving shorter duration of treatment. Since 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 probabilistic sensitivity analysis, including the interpretation of the cost-effectiveness acceptability curves (CEACs).

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

RCT		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Yu *et al*., 2007[55]	Standard (24 weeks)	7,834	20.82	15.64	
	Shortened (16 wks)	5,728	20.86	15.72	
	Incremental	-2,107	0.04	0.08	Shortened duration dominates
von Wagner *et al*.[56]	Standard (24 weeks)	10,089	20.61	15.31	
	Shortened (16 wks)	6,943	20.75	15.54	
	Incremental	-3,146	0.14	0.23	Shortened duration dominates

In both 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 £2,100 and £3,150. 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 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 due to structural uncertainties in the model, uncertainties over the composition of the baseline cohort and uncertainty over parameter values.

The DSA 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 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 to -0.08 at a starting age of 55 (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 -£4,807 at a starting age of 40 to -£5,098 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 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 cirrhotic patients.

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

	Genotype 1					
	Liu *et al.*[53]			**Yu *et al.*, 2008[54]**		
	Incr cost (£)	**Incr QALY**	**ICER**	**Incr cost (£)**	**Incr QALY**	**ICER**
Base case	-4,807	-0.14	34,510	-5,212	-0.08	64,880
Structural uncertainty						
Spontaneous SVR from mild (0.002)	-4,851	-0.13	37,420	-5,241	-0.07	70,779
Spontaneous SVR from mild (0.010)	-4,831	-0.13	36,033	-5,228	-0.08	67,953
Discount cost and outcome at 0%	-3,605	-0.38	9,543	-4,429	-0.24	18,785
Discount cost at 6%, outcome at 1.5%	-5,187	-0.24	21,447	-5,460	-0.15	37,096
Baseline cohort characteristics						

Cohort 80% male	-4,813	-0.14	34,917	-5,216	-0.08	65,702
Cohort 40% male	-4,788	-0.14	33,281	-5,200	-0.08	62,412
Change average age of cohort at start of simulation (base case 40 years old)						
-10 years	-4,674	-0.18	26,429	-5,126	-0.10	48,901
+ 5 years	-4,892	-0.12	41,051	-5,268	-0.07	78,362
+10 years	-4,989	-0.10	50,551	-5,331	-0.05	98,940
+15 years	-5,098	-0.08	65,021	-5,402	-0.04	132,866
Change distribution of cohort across disease stages at start of simulation						
Cohort 100% mild chronic HCV	-5,396	-0.09	57,661	-5,597	-0.05	110,708
Cohort 100% moderate HCV	-4,415	-0.17	26,641	-4,957	-0.10	50,807
Cohort 100% compensated cirrhosis	-3,817	-0.23	16,371	-4,567	-0.14	32,270
Parameter uncertainty						
Assume SVR is 25% lower in patients with compensated cirrhosis	-4,860	-0.13	36,627	-5,247	-0.08	69,001
Assume SVR is 50% lower in patients with compensated cirrhosis	-4,914	-0.13	38,964	-5,282	-0.07	73,614
Cohort 100% compensated cirrhosis, assume SVR is 25% lower in patients with compensated cirrhosis	-4,356	-0.17	26,023	-4,918	-0.10	49,855
Cohort 100% compensated cirrhosis, assume SVR is 50% lower in patients with compensated cirrhosis	-4,894	-0.10	48,177	-5,269	-0.06	94,485
Transition probability from mild to moderate disease	-4,733	-0.15	31,168	-5,164	-0.09	58,333
Transition probability from moderate disease to compensated cirrhosis	-4,650	-0.18	26,516	-5,110	-0.10	49,205
Cost of SVR state = £0	-4,790	-0.14	34,392	-5,201	-0.08	64,747
Reduce cost of PEG2a by 20%	-4,197	-0.14	30,136	-4,603	-0.08	57,298
Reduce cost of PEG2a by 30%	-3,893	-0.14	27,949	-4,298	-0.08	53,506
Reduce cost of RBV by 20%	-4,273	-0.14	30,681	-4,679	-0.08	58,242
Reduce cost of RBV by 20%	-4,007	-0.14	28,766	-4,412	-0.08	54,922

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

	Genotype 2			Genotype 2 / 3		
	Yu *et al.*, 2007[55]			von Wagner *et al.*[56]		
	Incr cost (£)	Incr QALY	ICER	Incr cost (£)	Incr QALY	ICER
Base case	-2,107	0.08	-26,000	-3,146	0.23	-13,555
Structural uncertainty						
Spontaneous SVR from mild (0.002)	-2,088	0.08	-27,124	-3,088	0.22	-14,071
Spontaneous SVR from mild (0.010)	-2,096	0.08	-26,595	-3,115	0.23	-13,827
Discount cost and outcome at 0%	-2,610	0.18	-14,416	-4,722	0.55	-8,664
Discount cost at 6%, outcome at 1.5%	-1,947	0.12	-15,695	-2,647	0.37	-7,220
Baseline cohort characteristics						
Cohort 80% male	-2,104	0.08	-26,165	-3,138	0.23	-13,632
Cohort 40% male	-2,115	0.08	-25,495	-3,171	0.24	-13,319
Change average age of cohort at start of simulation (base case 40 years old)						
-10 years	-2,162	0.10	-22,343	-3,320	0.28	-11,801
+ 5 years	-2,071	0.07	-28,532	-3,034	0.21	-14,752
+10 years	-2,030	0.06	-31,720	-2,906	0.18	-16,250
+15 years	-1,984	0.06	-35,763	-2,763	0.15	-18,153
Change distribution of cohort across disease stages at start of simulation						
Cohort 100% mild chronic HCV	-1,859	0.06	-30,058	-2,372	0.17	-13,780
Cohort 100% moderate HCV	-2,271	0.09	-24,655	-3,660	0.27	-13,721
Cohort 100% compensated cirrhosis	-2,522	0.12	-20,940	-4,444	0.36	-12,507
Parameter uncertainty						
Assume SVR is 25% lower in patients with compensated cirrhosis	-2,084	0.08	-26,629	-3,075	0.22	-13,763
Assume SVR is 50% lower in patients with compensated cirrhosis	-2,061	0.08	-27,303	-3,005	0.21	-13,987
Cohort 100% compensated cirrhosis, assume SVR is 25% lower in patients with compensated cirrhosis	-2,296	0.09	-24,734	-3,737	0.27	-13,895
Cohort 100% compensated cirrhosis, assume SVR is 50% lower in patients with compensated cirrhosis	-2,070	0.07	-31,740	-3,031	0.18	-16,594
Transition probability from mild to moderate disease	-2,137	0.09	-24,769	-3,243	0.25	-13,045
Transition probability from moderate disease to	-2,172	0.10	-22,591	-3,352	0.28	-11,994

compensated cirrhosis						
Cost of SVR state = £0	-2,113	0.08	-26,085	-3,168	0.23	-13,648
Reduce cost of PEG2a by 20%	-1,903	0.08	-23,494	-2,943	0.23	-12,680
Reduce cost of PEG2a by 30%	-1,802	0.08	-22,241	-2,842	0.23	-12,243
Reduce cost of RBV by 20%	-1,988	0.08	-24,537	-3,028	0.23	-13,045
Reduce cost of RBV by 20%	-1,929	0.08	-23,806	-2,968	0.23	-12,789

Since 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 counter-intuitive 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 (see Table 48).

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

Genotype 1	**Incremental Cost (£)**	**Incremental QALY**	**ICER**
SVR difference = 0%	-5,971	0.03	-199,047
SVR difference = 1%	-5,759	0.00	6,442,219
SVR difference = 3%	-5,334	-0.06	85,091
SVR difference = 5%	-4,908	-0.12	39,435
Genotype 2/3	**Incremental Cost (£)**	**Incremental QALY**	**ICER**
SVR difference = 0%	-1,618	0.01	-161,785
SVR difference = 1%	-1,405	-0.02	67,257
SVR difference = 3%	-980	-0.08	11,854
SVR difference = 5%	-555	-0.14	3,841

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.

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 α-2a and ribavirin

combination therapy is generally associated with reduced QALYs. For genotype 1 patients incremental QALYs associated with shortened duration of treatment are 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], whilst none of the simulations result in negative incremental QALYs using efficacy data from von Wagner and colleagues.[56] Incremental costs associated with shortened duration of treatment are negative in all simulations – ranging from -£2,500 to -£6,000 for genotype 1 patients and from -£550 to -£5,200 for genotype 2/3 patients. Table 49 reports summary information for the PSAs and Figure 3 to Figure 6 show the scatterplots for each analysis, including 95% confidence ellipses.

Table 49 Mean costs and outcomes (percentile-based 95% confidence intervals) for shortened treatment duration using peginterferon α-2a and ribavirin combination therapy from probabilistic sensitivity analysis

RCT		Lifetime Costs (£)	QALYs
Genotype 1 Liu *et al*.[53]	Standard duration	14,566 (14,020 to 15,708)	15.60 (14.39 to 16.77)
	Shortened duration	9,815 (8,546 to 12,040)	15.45 (14.32 to 16.56)
	Incremental	-4,752 (-5,582 to -3,658)	-0.14 (-0.32 to -0.02)
Genotype 1 Yu *et al*., 2008[54]	Standard duration	15,062 (14,067 to 17,639)	15.55 (14.38 to 16.71)
	Shortened duration	9,701 (8,309 to 12,538)	15.50 (14.36 to 16.66)
	Incremental	-5,361 (-5,810 to -4,922)	-0.06 (-0.13 to 0.01)
Genotype 2 Yu *et al*., 2007[55]	Standard duration	8,056 (7,360 to 9,300)	15.61 (14.48 to 16.78)
	Shortened duration	6,201 (5,577 to 7,659)	15.65 (14.49 to 16.84)
	Incremental	-1,855 (-2,019 to -1,576)	0.04 (0.00 to 0.07)
Genotypes 2/3 von Wagner *et al*.[56]	Standard duration	10,072 (8,048 to 13,552)	15.33 (14.25 to 16.42)
	Shortened duration	6,931 (5,794 to 9,160)	15.56 (14.41 to 16.66)
	Incremental	-3,141 (-4,287 to -2,242)	0.23 (0.08 to 0.40)

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

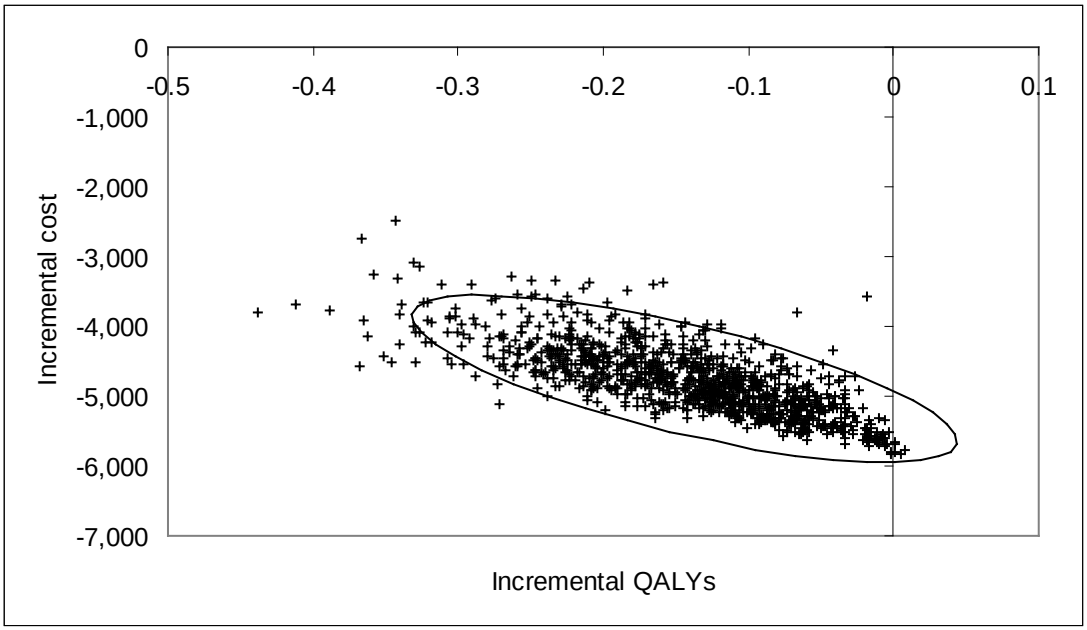


Figure 4 Cost-effectiveness plane for genotype 1 patients - incremental cost and incremental QALYs for shortened treatment duration using peginterferon α-2a and ribavirin combination therapy (24 vs 48 weeks of treatment) – efficacy from Yu *et al.*, 2008[54]

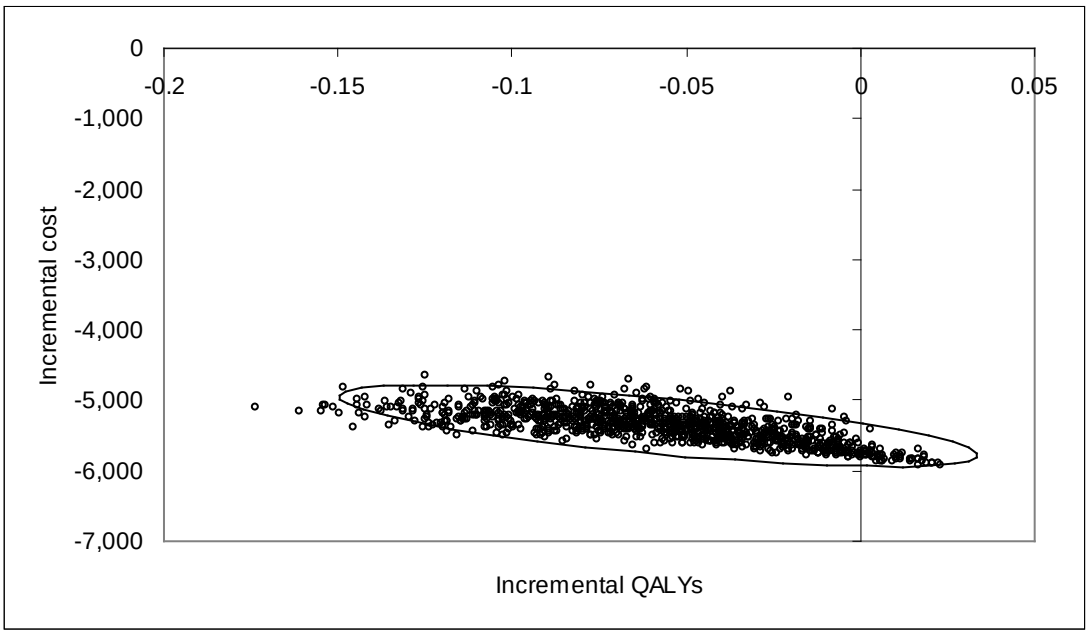


Figure 5 Cost-effectiveness plane for genotype 2 patients - incremental cost and incremental QALYs for shortened treatment duration using peginterferon α-2a and ribavirin combination therapy (16 vs 24 weeks of treatment) – efficacy from Yu *et al.*, 2007[55]

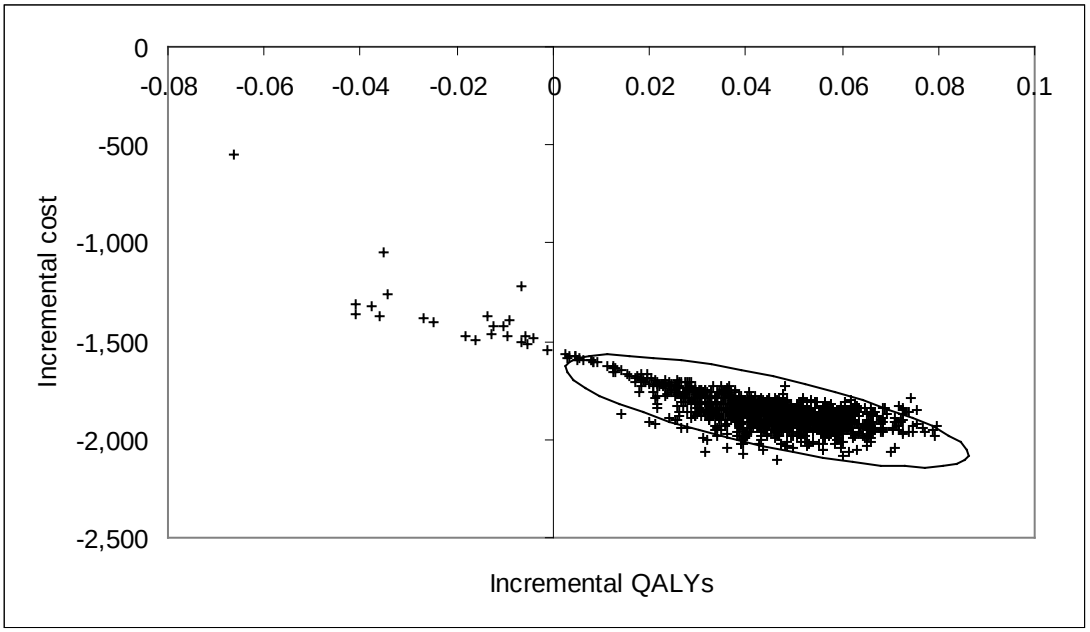
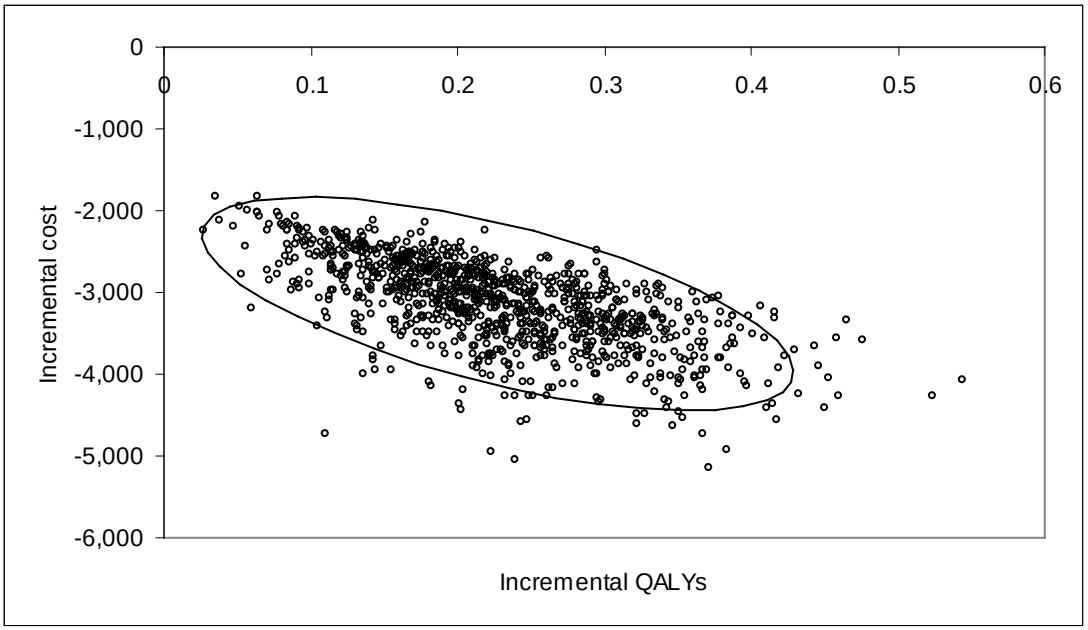


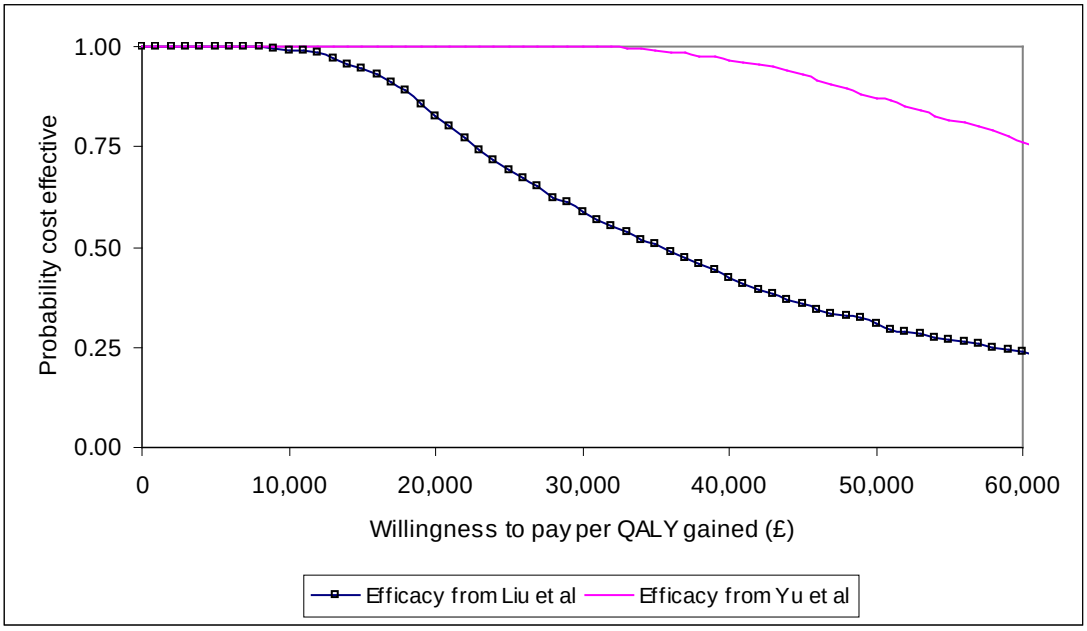
Figure 6 Cost-effectiveness plane for genotypes 2 / 3 patients - incremental cost and incremental QALYs for shortened treatment duration using peginterferon α-2a and ribavirin combination therapy (16 vs 24 weeks of treatment) – efficacy from von Wagner *et al.*[56]



In this analysis shortened duration of treatment using peginterferon α-2a and ribavirin combination therapy for genotype 1 patients had a probability of being cost-effective

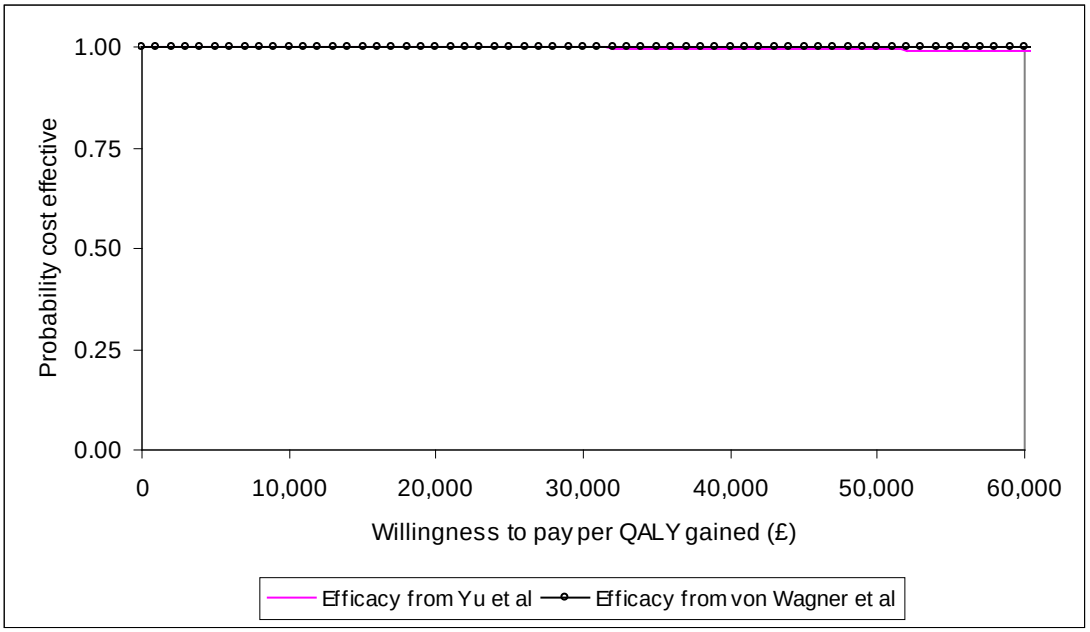
(compared with the standard duration (48 weeks) of treatment) of 83% at a willingness to pay threshold of £20,000 per QALY and 59% at a willingness to pay threshold of £30,000, using efficacy data from the trial reported by Liu and colleagues[53] (see Figure 7). The equivalent values using efficacy data from the trial reported by Yu and colleagues, 2008[54] are 100% at a willingness to pay threshold of £20,000 per QALY and at a willingness to pay threshold of £30,000.

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



For patients with genotypes 2/3, the probability of being cost-effective (compared with the standard duration (24 weeks) of treatment) was 100% at a willingness to pay threshold of £20,000 per QALY 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] (see 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 Figure 5 and Figure 6.

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



Peginterferon α-2b

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

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

RCT		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Berg *et al.*[59]	Standard (48 wks)	26,169	19.74	13.89	
	Shortened (24 wks)	17,173	20.03	14.38	
	Incremental	-8,996	0.29	0.49	Shortened duration dominates

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 £9,000. 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 deterministic sensitivity analysis for genotype 1 patients eligible for shortened treatment duration with peginterferon α-2b and ribavirin combination therapy. The deterministic sensitivity analyses 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.

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

	Genotype 1		
	Incremental cost (£)	**Incremental QALY**	**ICER**
Base case	8,996	-0.49	-18,190
Structural uncertainty			
Spontaneous SVR from mild (0.002)	8,874	-0.47	-18,957
Spontaneous SVR from mild (0.010)	8,930	-0.48	-18,595
Discount cost and outcome at 0%	12,292	-1.15	-10,697
Discount cost at 6%, outcome at 1.5%	7,952	-0.78	-10,247
Baseline cohort characteristics			
Cohort 80% male	8,979	-0.49	-18,303
Cohort 40% male	9,048	-0.51	-17,843
Change average age of cohort at start of simulation (base case 40 years old)			
-10 years	9,361	-0.60	-15,663
+ 5 years	8,762	-0.44	-19,944
+10 years	8,495	-0.38	-22,168
+15 years	8,196	-0.33	-25,024
Change distribution of cohort across disease stages at start of simulation			
Cohort 100% mild chronic HCV	7,377	-0.37	-19,983
Cohort 100% moderate HCV	10,072	-0.57	-17,760
Cohort 100% compensated cirrhosis	11,711	-0.75	-15,567
Parameter uncertainty			
Assume SVR is 25% lower in patients with compensated cirrhosis	8,848	-0.48	-18,569
Assume SVR is 50% lower in patients with compensated cirrhosis	8,701	-0.46	-18,978
Cohort 100% compensated cirrhosis, assume SVR is 25% lower in patients with compensated cirrhosis	10,233	-0.57	-17,899

Cohort 100% compensated cirrhosis, assume SVR is 50% lower in patients with compensated cirrhosis	8,755	-0.39	-22,384
Transition probability from mild to moderate disease	9,198	-0.53	-17,386
Transition probability from moderate disease to compensated cirrhosis	9,426	-0.59	-15,880
Cost of SVR state = £0	9,041	-0.49	-18,281
Reduce cost of PEG 2a by 20%	8,216	-0.49	-16,612
Reduce cost of PEG 2a by 30%	7,825	-0.49	-15,823
Reduce cost of RBV by 20%	8,669	-0.49	-17,527
Reduce cost of RBV by 20%	8,505	-0.49	-17,196

Since the included trial by Berg and colleagues[59] gives a potentially counter-intuitive 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 (see 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 52 Scenario analyses for difference in SVR for shortened treatment duration using peginterferon α-2b and ribavirin combination therapy, compared with standard treatment - impact on cost-effectiveness estimates

Genotype 1	Incremental Cost (£)	Incremental QALY	ICER
SVR difference = 0%	-5,971	0.03	-193,313
SVR difference = 1%	-5,759	0.00	6,249,786
SVR difference = 3%	-5,334	-0.06	82,347
SVR difference = 5%	-4,908	-0.12	38,053

Probabilistic sensitivity analysis

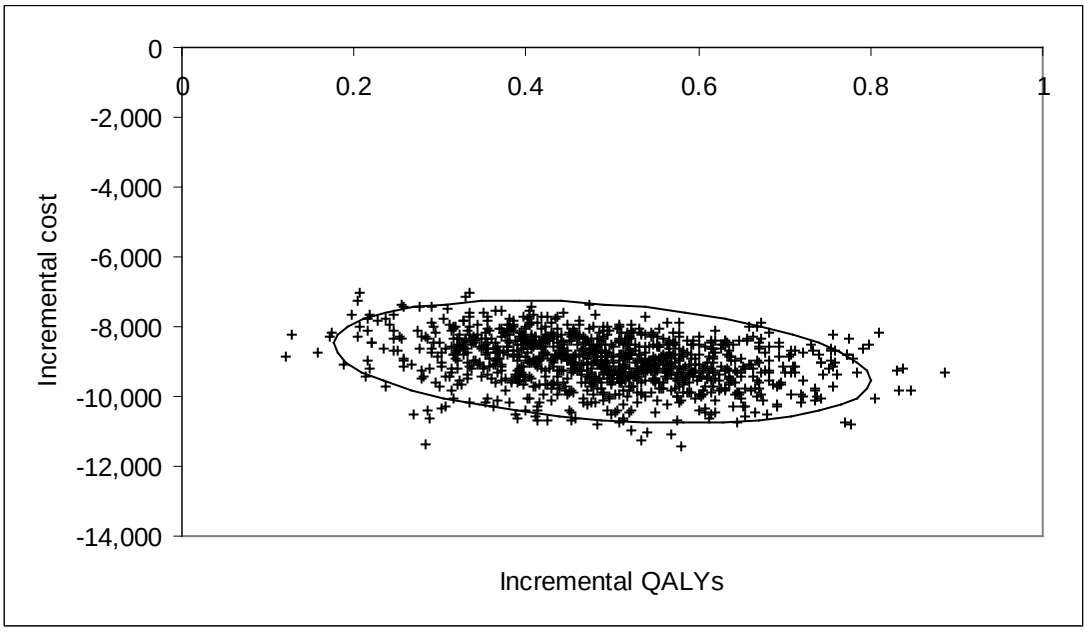
In a PSA, where the probabilities of achieving SVR, health state costs, health state utility values, and transition probabilities for the natural history parameters were sampled probabilistically, shortened duration of treatment with peginterferon α-2b and ribavirin combination therapy, for genotype 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.

Table 53 Mean costs and outcomes (percentile-based 95% confidence intervals) for shortened treatment duration using peginterferon α-2b and ribavirin combination therapy from probabilistic sensitivity analysis

RCT		Lifetime Costs (£)	QALYs
Berg *et al.*[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	-9,009 (-10,506 to -7,717)	0.49 (0.25 to 0.75)

Figure 9 Cost-effectiveness plane for genotype 1 patients - incremental cost and incremental QALYs for shortened treatment duration using peginterferon α-2b and ribavirin combination therapy (24 vs 48 weeks of treatment) – efficacy from Berg and colleagues[59]



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

5.4.2 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[101] as this group of patients are expected to be

older and will likely have with more advanced liver disease than would be the case for treatment-naïve groups.

Peginterferon α-2a

SVRs for this patient population are taken from the RCT reported by Jensen and colleagues[87] which compared re-treatment with varying doses and duration of peginterferon α-2a in patients who had previously failed to respond to, or relapsed on, pegylated or non-peginterferon alfa and 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 α-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 α-2a and ribavirin combination therapy are presented in Table 54. This table reports total costs (anti-viral treatment and supportive care), health outcomes (in terms of life years and QALYs) and the incremental cost per QALYs ratios.

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

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per 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	6,419	0.54	0.59	10,926

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 £6,419 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 anti-viral treatment.

The cost-effectiveness results in Table 54 do not take account of patients withdrawing from treatment due to adverse events, nor do they consider the impact of treatment stopping rules (for example 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 due to adverse effects of treatment with peginterferon alfa and ribavirin combination therapy. This has a marginal impact on the cost-effectiveness results, with the ICER for patients with genotype 1 remaining high.

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

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per 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	6,267	0.54	0.59	10,650

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 £1,415 and £3,398, depending on genotype grouping, whilst also increasing the QALY gain by approximately 0.06 QALYs. As a result the ICER for patients with genotype 1 falls to £9,169.

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

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotype 1	BSC	26,221	16.75	10.74	
	Peg α-2a	29,619	17.07	11.11	
	Incremental	3,398	0.33	0.37	9,169
Genotype non-1	BSC	26,221	16.75	10.74	
	Peg α-2a	27,636	17.28	11.36	
	Incremental	1,415	0.54	0.62	2,294

The EVRs used in the analysis reported in Table 56 are taken from the Roche submission to NICE[104], since Jensen and colleagues[87] 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 only reports 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.

Deterministic sensitivity analysis

Table 57 reports the results of a DSA for re-treatment using peginterferon α-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.

The DSA 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 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 characterstics. 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 cirrhotic and non-cirrhotic patients. Subsequent analyses suggest that the ICER is also sensitive to variation in the SVR applied for patients with cirrhosis at baseline.

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

	Genotype 1			Genotype non-1		
	Incr cost (£)	**Incr QALY**	**ICER**	**Incr cost (£)**	**Incr QALY**	**ICER**
Base case	3,398	0.37	9,169	1,415	0.62	2,294
Structural uncertainty						
Spontaneous SVR from mild (0.002)	3,460	0.36	9,685	1,516	0.60	2,547
Spontaneous SVR from mild (0.010)	3,431	0.36	9,442	1,469	0.61	2,428
Discount cost and outcome at 0%	945	0.84	1,121	-2,588	1.39	-1,864
Discount cost at 6%, outcome at 1.5%	4,270	0.58	7,355	2,838	0.96	2,957
Baseline cohort characteristics						
Cohort 80% male	3,414	0.37	9,306	1,441	0.61	2,360
Cohort 40% male	3,348	0.38	8,754	1,334	0.64	2,097
Change average age of cohort at start of simulation (base case 40 years old)						
-10 years	3,052	0.47	6,500	851	0.78	1,093
+ 5 years	3,624	0.32	11,401	1,784	0.53	3,361
+10 years	3,887	0.26	14,685	2,213	0.44	4,983
+15 years	4,188	0.21	19,740	2,705	0.36	7,547
Change distribution of cohort across disease stages at start of simulation						
Cohort 100% mild chronic HCV	5,325	0.23	23,560	4,560	0.38	11,970
Cohort 100% moderate HCV	3,152	0.37	8,508	1,014	0.62	1,644
Cohort 100% compensated cirrhosis	1,680	0.52	3,232	-1,389	0.86	-1,614
Parameter uncertainty						
Assume SVR is 25% lower in patients with compensated cirrhosis	3,784	0.33	11,573	2,045	0.55	3,747
Assume SVR is 50% lower in patients with compensated cirrhosis	4,170	0.28	14,720	2,675	0.47	5,638
Cohort 100% compensated cirrhosis, assume SVR is 25% lower in patients with compensated cirrhosis	2,886	0.38	7,526	579	0.64	907
Cohort 100% compensated cirrhosis, assume SVR is 50% lower in patients with compensated cirrhosis	4,091	0.25	16,570	2,546	0.42	6,135
Transition probability from mild to moderate disease	3,288	0.39	8,462	1,236	0.65	1,912
Transition probability from moderate disease to compensated cirrhosis	3,126	0.43	7,313	971	0.71	1,368
Cost of SVR state = £0	3,360	0.37	9,066	1,353	0.62	2,193

Reduce cost of PEG2a by 20%	2,868	0.37	7,739	796	0.62	1,290
Reduce cost of PEG2a by 30%	2,603	0.37	7,024	486	0.62	787
Reduce cost of RBV by 20%	2,316	0.37	6,248	1,054	0.62	1,708
Reduce cost of RBV by 20%	2,161	0.37	5,831	873	0.62	1,415

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 α-2a and ribavirin combination therapy is associated with increased QALYs (with a range from 0.05 to 0.59 QALYs for genotype 1 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 (see Table 58 for summary information and Figure 10 and Figure 11 for scatterplots which 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% confidence intervals) for re-treatment using peginterferon α-2a and ribavirin combination therapy, from probabilistic sensitivity analysis

Genotype		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	3,369 (1,573 to 4,509)	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 (-4,127 to 4,030)	0.63 (0.14 to 1.49)

Figure 10 Cost-effectiveness plane for genotype 1 - incremental cost and incremental QALYs for re-treatment using peginterferon α-2a and ribavirin combination therapy (applying early stopping rule based on EVR)

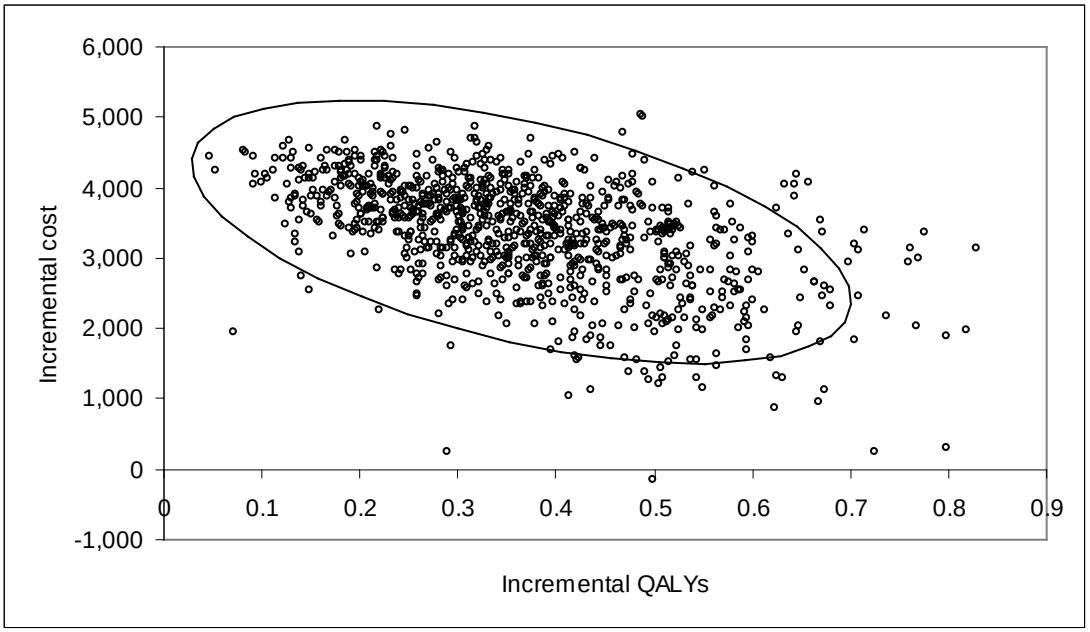
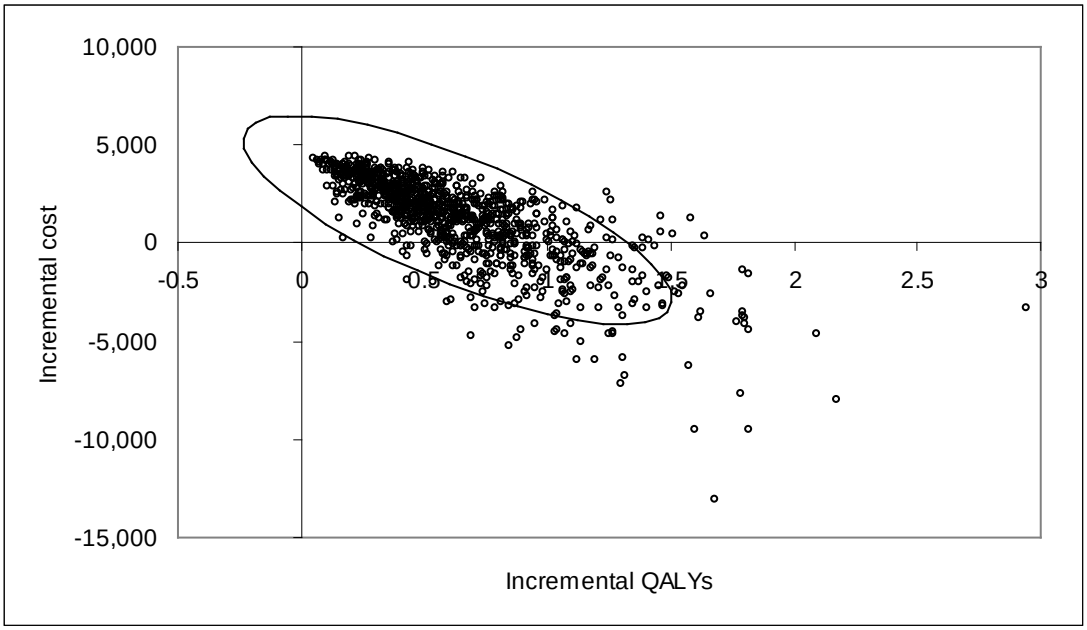


Figure 11 Cost-effectiveness plane for genotype non-1 - incremental cost and incremental QALYs for re-treatment using peginterferon α-2a and ribavirin combination therapy (applying early stopping rule based on EVR)



In this analysis, re-treatment using peginterferon alfa and ribavirin combination therapy for genotype 1 patients had 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% (see Figure 12). For genotype non-1 patients the probability of re-treatment using peginterferon alfa and 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 (see Figure 13).

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

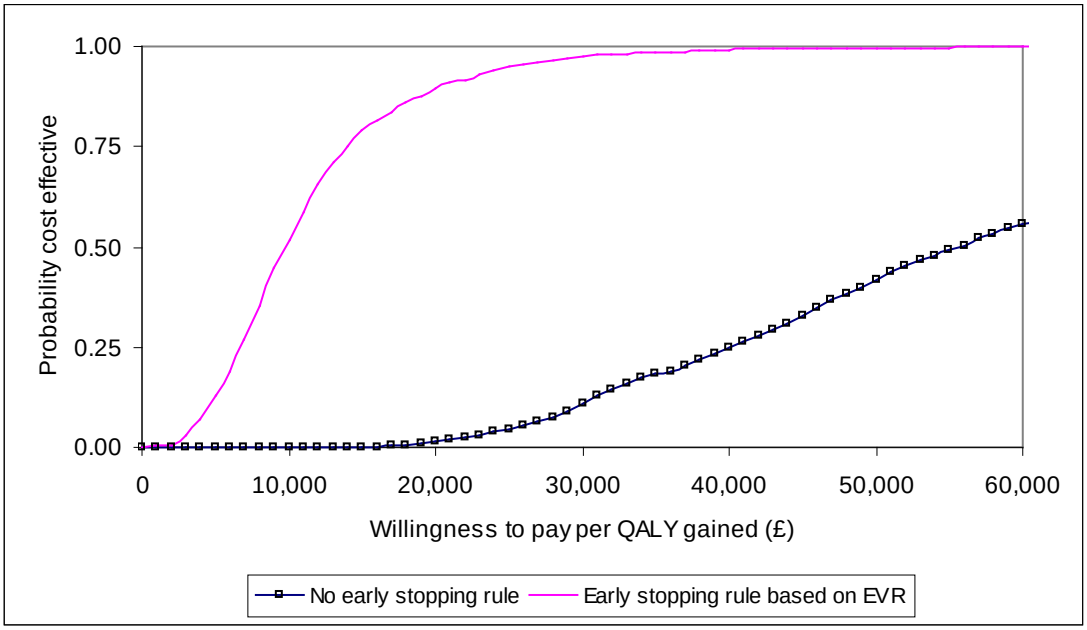
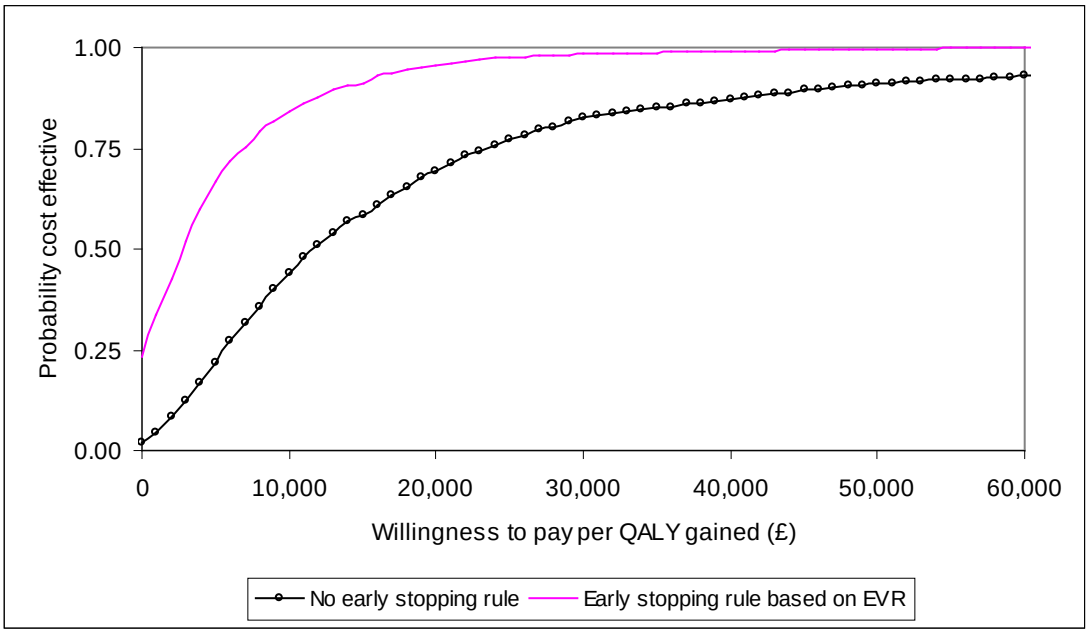


Figure 13 Cost-effectiveness acceptability curves for re-treatment of genotype non-1 patients with peginterferon α-2a, with and without stopping rules based on EVR



Peginterferon α-2b

SVRs for this patient population are taken from the MS by Schering-Plough, which reported treatment outcomes for the EPIC3 study[94] (a multi-centre, 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 α-2b and ribavirin combination therapy are presented in Table 59. This table reports total costs (anti-viral treatment and supportive care), health outcomes (in terms of life years and QALYs) and the incremental cost per QALYs ratios.

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

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotypes 1+4	BSC	26,221	16.75	10.74	
	Peg α-2b	35,601	17.12	11.14	
	Incremental	9,380	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

The impact of re-treating this group of patients is to improve the predicted outcome (by 0.39 and 1.72 QALYs for genotype 1+4 and genotype 2+3, respectively) and to increase lifetime costs (by £9,380 for genotype 1+4). The reduction in supportive care costs associated with disease progression in genotype 2+3 patients, associated with re-treatment with peginterferon α-2b and ribavirin combination therapy, is sufficient to fully offset the additional costs of anti-viral 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, in the MS.

The cost-effectiveness results in Table 59 do not take account of patients withdrawing from treatment due to adverse events, nor do they consider the impact of treatment stopping rules (for example 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 due to adverse effects of treatment with peginterferon α-2b and ribavirin combination therapy – this has a marginal impact on the cost-effectiveness results.

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

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotypes 1+4	BSC	26,221	16.75	10.74	
	Peg α-2b	35,417	17.12	11.14	
	Incremental	9,197	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	-1,173	1.47	1.72	Peg α-2b dominates

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+4 patients treated with peginterferon α-2b and ribavirin combination therapy to £3,256. As a result the ICER for patients with genotype 1 falls to £7,681.

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

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotypes 1+4	BSC	26,221	16.75	10.74	
	Peg α-2b	29,476	17.12	11.17	
	Incremental	3,256	0.37	0.42	7,681
Genotypes 2+3	BSC	26,221	16.75	10.74	
	Peg α-2b	23,371	18.21	12.47	
	Incremental	-2,850	1.47	1.73	Peg α-2b dominates

Deterministic sensitivity analysis

Table 62 reports the results of a DSA for re-treatment using peginterferon α-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 other variables unchanged. The DSA 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 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 patient 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+4 patients and results in a positive, though low value, ICER for genotype 2+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+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 α-2b and ribavirin combination therapy in previously treated patients – applying early stopping rule for patients not demonstrating an EVR

	Genotype 1 + 4			Genotype 2 + 3		
	Incr cost (£)	**Incr QALY**	**ICER**	**Incr cost (£)**	**Incr QALY**	**ICER**
Base case	3,256	0.42	7,681	-2,850	1.73	-1,650
Structural uncertainty						
Spontaneous SVR from mild (0.002)	3,326	0.41	8,139	-2,575	1.67	-1,545
Spontaneous SVR from mild (0.010)	3,294	0.42	7,923	-2,702	1.69	-1,594
Discount cost and outcome at 0%	460	0.96	477	-13,840	3.84	-3,600
Discount cost at 6%, outcome at 1.5%	4,250	0.66	6,408	1,055	2.67	396
Baseline cohort characteristics						
Cohort 80% male	3,274	0.42	7,802	-2,778	1.71	-1,624
Cohort 40% male	3,199	0.44	7,313	-3,073	1.78	-1,726
Change average age of cohort at start of simulation (base case 40 years old)						
-10 years	2,862	0.54	5,331	-4,399	2.17	-2,027
+ 5 years	3,514	0.36	9,658	-1,837	1.49	-1,232
+10 years	3,813	0.30	12,579	-660	1.25	-527
+15 years	4,156	0.24	17,087	690	1.02	678
Change distribution of cohort across disease stages at start of simulation						
Cohort 100% mild chronic HCV	5,453	0.26	21,048	5,783	1.08	5,359
Cohort 100% moderate HCV	2,976	0.42	7,022	-3,951	1.73	-2,289
Cohort 100% compensated	1,297	0.59	2,184	-	2.40	-4,402

cirrhosis				10,548		
Parameter uncertainty						
Assume SVR is 25% lower in patients with compensated cirrhosis	3,696	0.37	9,878	-1,121	1.53	-732
Assume SVR is 50% lower in patients with compensated cirrhosis	4,136	0.32	12,751	607	1.34	455
Cohort 100% compensated cirrhosis, assume SVR is 25% lower in patients with compensated cirrhosis	2,672	0.44	6,093	-5,146	1.78	-2,884
Cohort 100% compensated cirrhosis, assume SVR is 50% lower in patients with compensated cirrhosis	4,046	0.28	14,304	255	1.17	218
Transition probability from mild to moderate disease	3,131	0.44	7,044	-3,342	1.81	-1,849
Transition probability from moderate disease to compensated cirrhosis	2,946	0.49	6,028	-4,069	1.98	-2,053
Cost of SVR state = £0	3,213	0.42	7,578	-3,020	1.73	-1,749
Reduce cost of PEG2b by 20%	2,518	0.42	5,940	-4,161	1.73	-2,409
Reduce cost of PEG2b by 30%	2,149	0.42	5,069	-4,816	1.73	-2,789
Reduce cost of RBV by 20%	2,946	0.42	6,950	-3,400	1.73	-1,969
Reduce cost of RBV by 20%	2,791	0.42	6,584	-3,675	1.73	-2,128

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 genotype 1+4 and from 0.28 to 3.06 QALYs for genotype 2+3 patients), but for genotype 1+4 patients is typically also associated with increased costs when compared with BSC (see Table 63 for summary information and Figure 14 and Figure 15 for scatterplots which also shows the 95% confidence ellipses). The incremental cost was negative in approximately 84% of simulations for genotype 2+3 patients.

Table 63 Mean costs and outcomes (percentile-based 95% confidence intervals) for re-treatment using peginterferon α-2b and ribavirin combination therapy, from probabilistic sensitivity analysis

Genotype		Lifetime Costs (£)	QALYs
Genotype 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	3,298 (1,785 to 4,480)	0.42 (0.22 to 0.66)
Genotype 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	-2,664 (-8,971 to 1,846)	1.69 (0.88 to 2.48)

Figure 14 Cost-effectiveness plane for genotype 1 + 4 - incremental cost and incremental QALYs for re-treatment using peginterferon α-2b and ribavirin combination therapy (applying early stopping rule based on EVR)

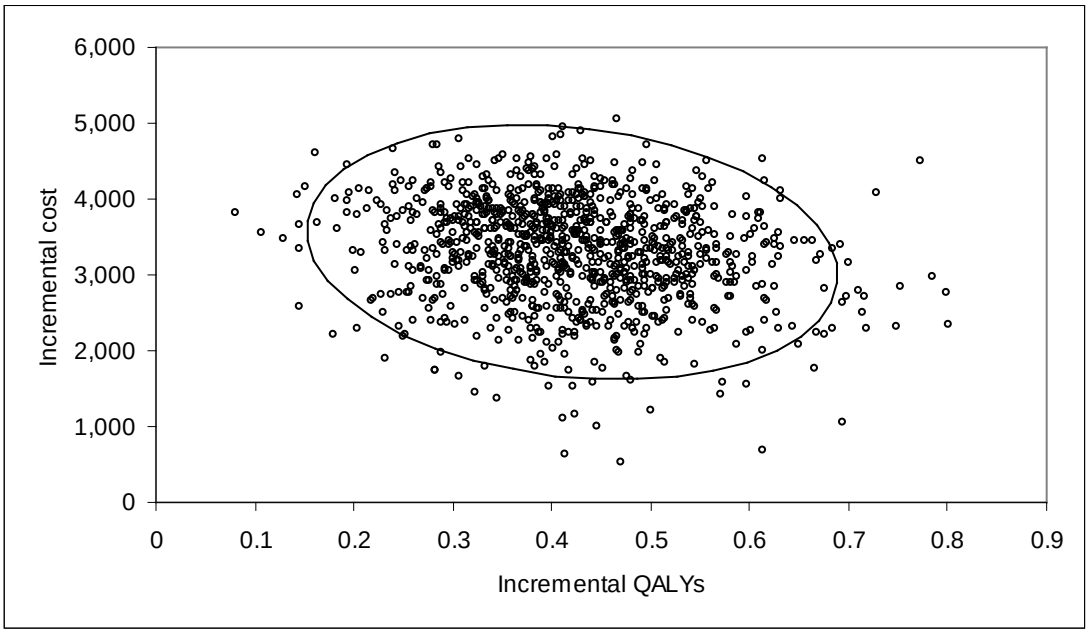
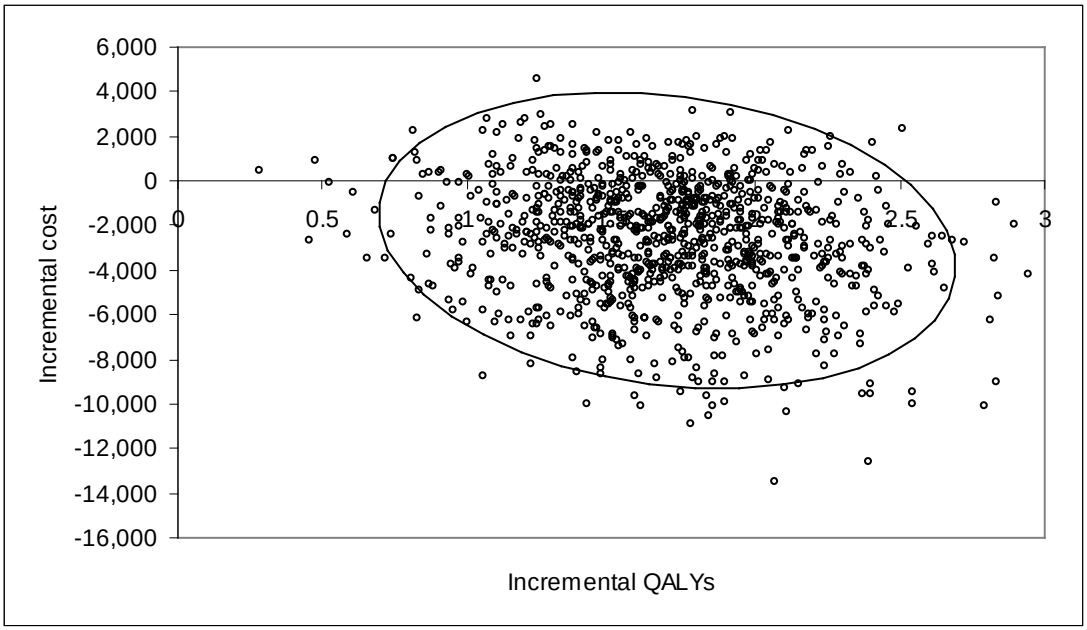


Figure 15 Cost-effectiveness plane for genotype 2 + 3 - incremental cost and incremental QALYs for re-treatment using peginterferon α-2b and ribavirin combination therapy (applying early stopping rule based on EVR)



In this analysis, re-treatment using peginterferon α-2b and ribavirin combination therapy for genotype 1+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 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% (see Figure 16). For genotype 2+3 patients the probability of re-treatment using peginterferon α-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 (see Figure 17).

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

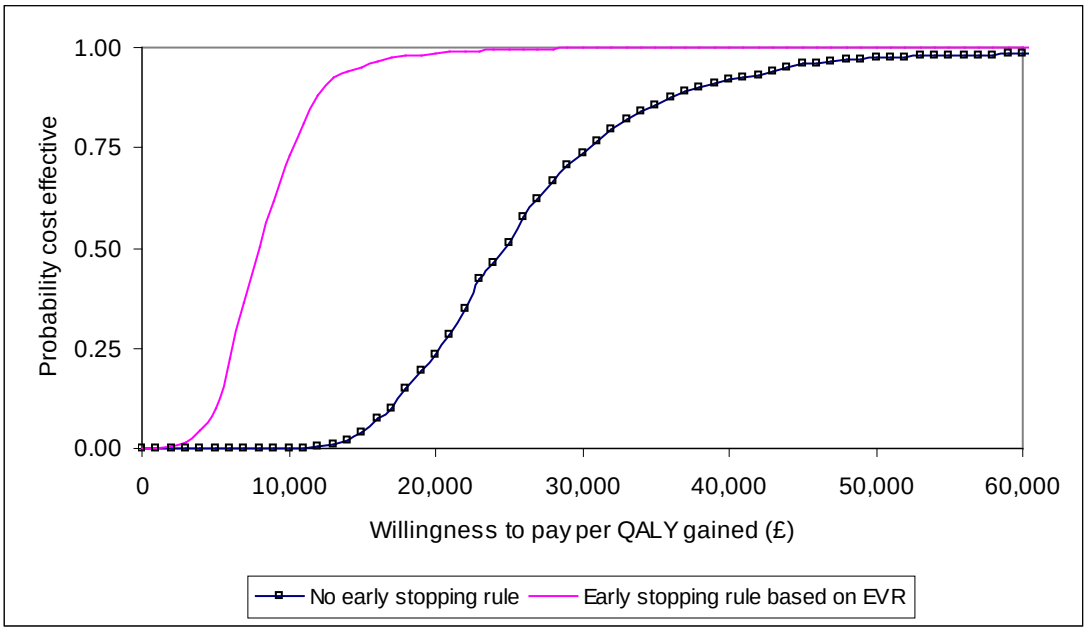
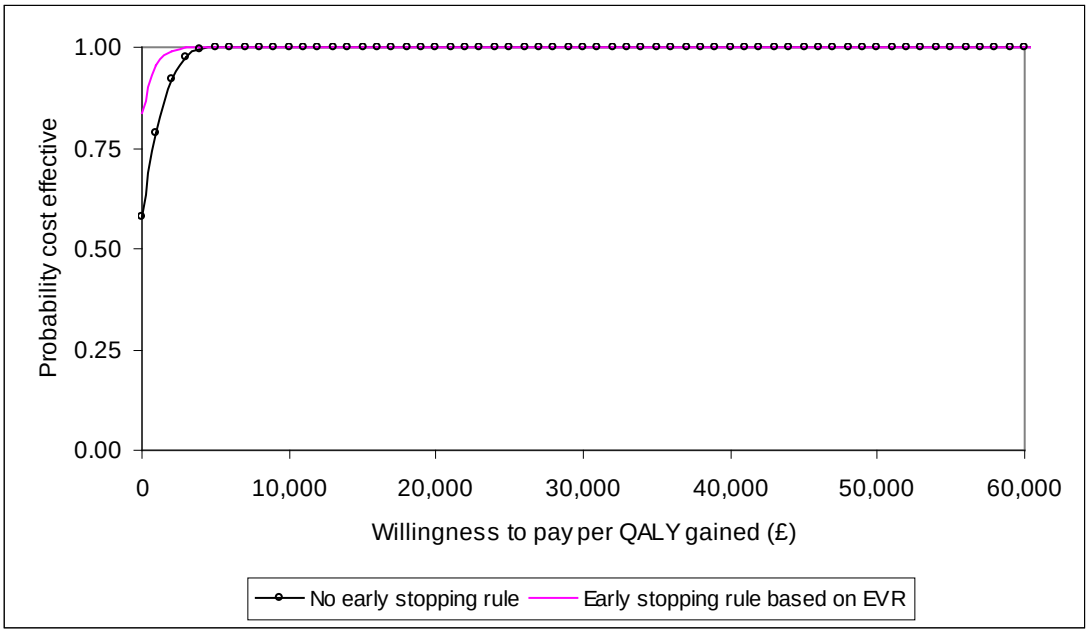


Figure 17 Cost-effectiveness acceptability curves for re-treatment of genotype 2+3 patients with peginterferon α-2b, with and without stopping rules based on EVR



5.4.3 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.[101] SVRs for this patient population are based on those reported in two recent systematic reviews of anti-viral treatment with peginterferon alfa in HCV/HIV co-infected patients, which included trials with active treatment comparators[50,51] (see Appendix 8). The systematic review of clinical-effectiveness in this report (Section 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 (anti-viral 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 α-2a[42] and for peginterferon α-2b.[43]

Peginterferon α-2a

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

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

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	Peg α-2a	28,133	19.43	13.40	
	Incremental	5,932	0.51	0.75	7,941
Genotypes 2 + 3	BSC	22,201	18.93	12.65	
	Peg α-2a	20,484	20.13	14.51	
	Incremental	-1,717	1.20	1.86	Peg α-2a dominates

The impact of treating this group is to improve the predicted outcome (by 0.75 and 1.86 QALYs for genotype 1+4 and genotypes 2+3, respectively) and to increase lifetime costs for patients with genotype 1+4 (by £5,932). However in patients with genotypes 2+3 the modelled reduction in supportive care costs (in the peginterferon treated cohort) offsets the

additional costs of anti-viral treatment – in this situation the strategy of providing anti-viral 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 a RR for cirrhosis of 2.07 (95% confidence interval 1.4 to 3.07) and a RR for decompensation of 6.14 (95% confidence interval 2.86 to 13.20) in HCV/HIV co-infected patients compared with 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 α-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 65 Cost-effectiveness of treatment of HCV/HIV co-infected patients with peginterferon α-2a and ribavirin combination therapy – using higher fibrosis progression probability for co-infected patients

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotypes 1 + 4	BSC	31,839	16.91	10.90	
	Peg α-2a	35,254	17.94	12.10	
	Incremental	3,415	1.03	1.21	2,833
Genotypes 2 + 3	BSC	31,839	16.91	10.90	
	Peg α-2a	24,137	19.37	13.84	
	Incremental	-7,703	2.46	2.95	Peg α-2a dominates

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 expectancy at age 40 of 33.2 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 α-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 + 3 patients.

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

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotypes 1 + 4	BSC	19,865	17.46	11.70	
	Peg α-2a	26,398	17.84	12.31	
	Incremental	6,534	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

Table 67 and Table 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 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 α-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 for mono-infected patients.

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

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	Peg α-2a	28,133	19.43	13.25	
	Incremental	5,932	0.51	0.60	9,889
Genotypes 2 + 3	BSC	22,201	18.93	12.65	
	Peg α-2a	20,484	20.13	14.16	
	Incremental	-1,717	1.20	1.51	Peg α-2a dominates

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

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	Peg α-2a	28,133	19.43	13.10	
	Incremental	5,932	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	-1,717	1.20	1.16	Peg α-2a dominates

A final scenario analysis was performed to consider the impact of on-treatment monitoring costs on the cost-effectiveness of anti-viral 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 α-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 + 3 patients.

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

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	Peg α-2a	29,184	19.43	13.40	
	Incremental	6,983	0.51	0.75	9,348
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

Deterministic sensitivity analysis

Table 70 reports the results of a DSA for treatment of HCV/HIV co-infected patients using peginterferon α-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.

The greatest variability in ICERs is associated with changes in the age at which patients enter the model, the distribution of patient across disease stages, (to a lesser extent) response to treatment (SVR) for patients with cirrhosis. For genotype 2+3 patients the ICER becomes positive (positive incremental cost and positive incremental QALYs) for the scenarios where age at entry is increased by ten 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+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+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.

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

	Genotype 1			Genotype 2 + 3		
	Incr cost (£)	**Incr QALY**	**ICER**	**Incr cost (£)**	**Incr QALY**	**ICER**
Base case	5,932	0.75	7,941	-1,717	1.86	-924
Structural uncertainty						
Spontaneous SVR from mild (0.002)	6,144	0.70	8,765	-1,213	1.75	-693
Spontaneous SVR from mild (0.010)	6,047	0.72	8,374	-1,445	1.80	-803
Discount cost and outcome at 0%	206	1.88	109	-15,331	4.56	-3,360
Discount cost at 6%, outcome at 1.5%	7,745	1.24	6,266	2,593	3.02	858
Baseline cohort characteristics						
Cohort 80% male	5,961	0.74	8,055	-1,648	1.84	-895
Cohort 40% male	5,842	0.77	7,598	-1,933	1.91	-1,012
Change average age of cohort at start of simulation (base case 40 years old)						
-10 years	5,299	0.93	5,722	-3,223	2.28	-1,411
+ 5 years	6,338	0.65	9,734	-752	1.63	-461
+10 years	6,804	0.55	12,291	354	1.40	253
+15 years	7,323	0.46	16,029	1,588	1.17	1,359
Change distribution of cohort across disease stages at start of simulation						
Cohort 100% mild chronic HCV	8,744	0.53	16,524	4,969	1.34	3,706
Cohort 100% moderate HCV	4,064	0.87	4,655	-6,159	2.16	-2,854

Cohort 100% compensated cirrhosis	1,217	1.19	1,018	-12,928	2.92	-4,423
Parameter uncertainty						
Assume SVR is 25% lower in patients with compensated cirrhosis	6,189	0.72	8,648	-1,107	1.78	-620
Assume SVR is 50% lower in patients with compensated cirrhosis	6,446	0.68	9,420	-496	1.71	-290
Cohort 100% compensated cirrhosis, assume SVR is 25% lower in patients with compensated cirrhosis	3,784	0.88	4,295	-6,825	2.18	-3,135
Cohort 100% compensated cirrhosis, assume SVR is 50% lower in patients with compensated cirrhosis	6,351	0.57	11,194	-721	1.43	-504
Transition probability from mild to moderate disease	5,581	0.81	6,916	-2,552	2.00	-1,275
Transition probability from moderate disease to compensatd cirrhosis	5,186	0.92	5,642	-3,492	2.27	-1,540
Cost of SVR state = £0	5,854	0.75	7,836	-1,904	1.86	-1,024
Reduce cost of PEG 2a by 20%	4,714	0.75	6,310	-2,935	1.86	-1,579
Reduce cost of PEG 2a by 30%	4,105	0.75	5,495	-3,545	1.86	-1,907
Reduce cost of RBV by 20%	5,221	0.75	6,989	-2,428	1.86	-1,306
Reduce cost of RBV by 20%	4,866	0.75	6,513	-2,784	1.86	-1,498

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 + 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 £9,022) when compared with BSC (see Table 71 and

Figure 18). While treatment for patients with genotypes 2 + 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 (see Figure 19).

Table 71 Mean costs and outcomes (percentile-based 95% confidence intervals) for HCV/HIV co-infected patients with peginterferon α-2a and ribavirin combination therapy, from probabilistic sensitivity analysis

Genotype		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	5,986 (3,332 to 7,993)	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	-1,575 (-7,275 to 2,673)	1.82 (0.91 to 2.81)

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

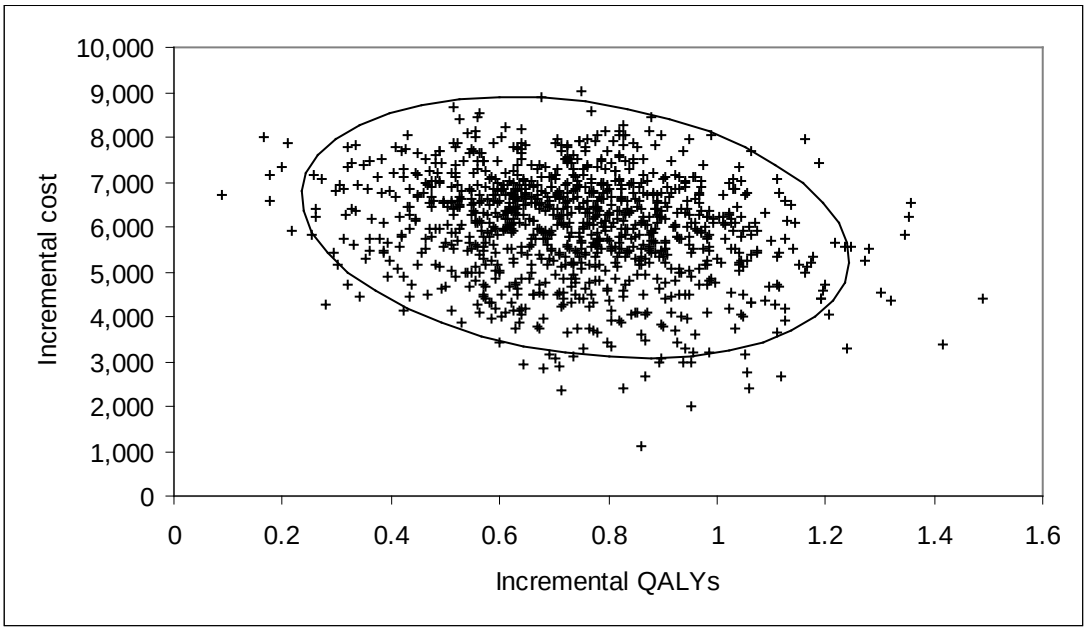
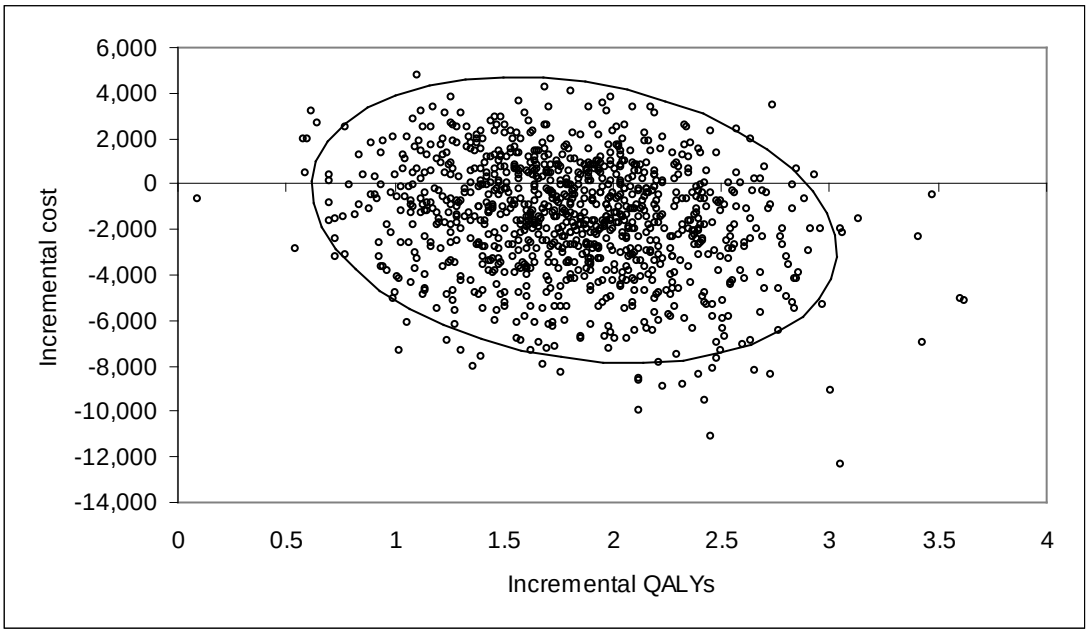


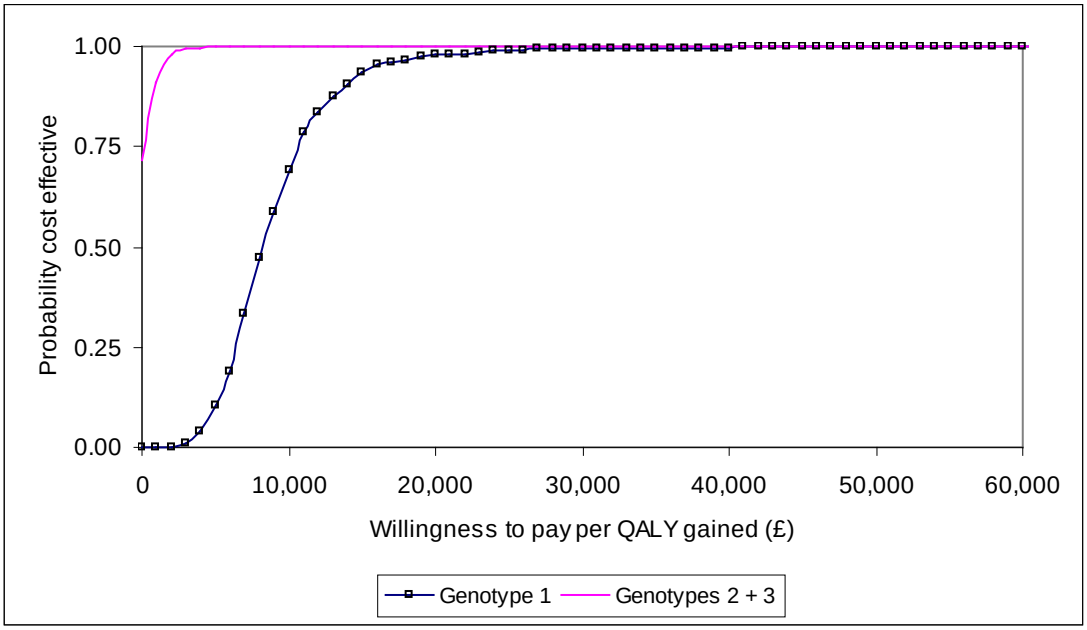
Figure 19 Cost-effectiveness plane for genotypes 2 + 3 - incremental cost and incremental QALYs for treatment of HCV/HIV co-infected patients with peginterferon α-2a and ribavirin combination therapy



In this analysis, treatment using peginterferon α-2a and ribavirin combination therapy, for HCV/HIV co-infected patients with genotypes 1 + 4, the 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 (see Figure 20). For patients with genotypes 2 + 3, treatment using peginterferon α-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 α-2a and ribavirin combination therapy



Peginterferon α-2b

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

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

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	Peg α-2b	30,102	19.38	13.32	
	Incremental	7,901	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	2,989	0.91	1.38	2,161

The impact of treating this group of patients is to improve the predicted outcome (by 0.67 and 1.38 QALYs for genotype 1+4 and genotypes 2+3, respectively) and to increase lifetime costs

(by £7,7901 and £2,989 QALYs for genotype 1+4 and genotypes 2+3, respectively). The reduction in supportive care costs associated with disease progression in both groups of patients (genotypes 1+4 and genotypes 2+3) is insufficient fully to offset the additional costs of anti-viral 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 relative risks for disease progression[25] to the baseline risks in the natural history model. This suggests that treatment using peginterferon α-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 α-2b is dominant (produces improved outcomes at lower cost) compared with supportive care for patients with genotypes 2 + 3.

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

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotypes 1 + 4	BSC	31,839	16.91	10.90	
	Peg α-2b	37,465	17.84	11.98	
	Incremental	5,626	0.93	1.08	5,193
Genotypes 2 + 3	BSC	31,839	16.91	10.90	
	Peg α-2b	30,327	18.76	13.10	
	Incremental	-1,513	1.85	2.20	Peg α-2b dominates

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 both for peginterferon treated and BSC cohorts and would suggest that treatment using peginterferon α-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.

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

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)

Genotypes 1 + 4	BSC	19,865	17.46	11.70	
	Peg α-2b	28,309	17.80	12.25	
	Incremental	8,445	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	4,065	0.68	1.14	3,570

Table 75 and Table 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 α-2b 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 for mono-infected patients.

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

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	Peg α-2b	30,102	19.38	13.19	
	Incremental	7,901	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	2,989	0.91	1.12	2,669

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

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	Peg α-2b	30,102	19.38	13.05	
	Incremental	7,901	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	2,989	0.91	0.86	3,489

A final scenario analysis was performed to consider the impact of on-treatment monitoring costs on the cost-effectiveness of anti-viral 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 α-2b and ribavirin combination therapy is less cost-effective than in the base case.

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

Genotype		Cost (£)	Outcome (Life years)	Outcome (QALYs)	ICER (£ per QALY gained)
Genotypes 1 + 4	BSC	22,201	18.93	12.65	
	Peg α-2b	31,153	19.38	13.32	
	Incremental	8,952	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	4,040	0.91	1.38	2,921

Deterministic sensitivity analysis

Table 78 reports the results of a DSA for treatment of HCV/HIV co-infected patients using peginterferon α-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 patient across disease stages, (to a lesser extent) response to treatment (SVR) for patients with cirrhosis. Increasing the age at which patients enter the model by 15 years leads to an approximate doubling of the ICER for genotype 1+4 patients – the QALY gain with treatment is reduced by around a half for both genotype 1+4 patients and genotype 2+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 diease states leads to more favourable cost-effectiveness results.

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

	Genotype 1			Genotype 2 + 3		
	Incr cost (£)	**Incr QALY**	**ICER**	**Incr cost (£)**	**Incr QALY**	**ICER**
Base case	7,901	0.67	11,806	2,989	1.38	2,161
Structural uncertainty						
Spontaneous SVR from mild (0.002)	8,093	0.63	12,893	3,369	1.30	2,590
Spontaneous SVR from mild (0.010)	8,005	0.65	12,376	3,194	1.34	2,386
Discount cost and outcome at 0%	2,727	1.70	1,607	-7,250	3.42	-2,122
Discount cost at 6%, outcome at 1.5%	9,539	1.11	8,586	6,231	2.26	2,760
Baseline cohort characteristics						
Cohort 80% male	7,927	0.66	11,957	3,041	1.37	2,219
Cohort 40% male	7,819	0.69	11,350	2,827	1.42	1,988
Change average age of cohort at start of simulation (base case 40 years old)						
-10 years	7,329	0.83	8,819	1,857	1.70	1,090
+ 5 years	8,268	0.58	14,192	3,715	1.21	3,066
+10 years	8,688	0.49	17,573	4,547	1.04	4,384
+15 years	9,157	0.41	22,499	5,475	0.86	6,336
Change distribution of cohort across disease stages at start of simulation						
Cohort 100% mild chronic HCV	10,442	0.47	22,104	8,018	0.99	8,070
Cohort 100% moderate HCV	6,213	0.78	7,934	-351	1.61	-218
Cohort 100% compensated cirrhosis	3,640	1.07	3,390	-5,443	2.18	-2,493
Parameter uncertainty						
Assume SVR is 25% lower in patients with compensated cirrhosis	8,133	0.64	12,690	3,448	1.33	2,599
Assume SVR is 50% lower in patients with compensated cirrhosis	8,365	0.61	13,656	3,907	1.27	3,075
Cohort 100% compensated cirrhosis, assume SVR is 25% lower in patients with compensated cirrhosis	5,960	0.79	7,541	-852	1.62	-525
Cohort 100% compensated cirrhosis, assume SVR is 50% lower in patients with compensated cirrhosis	8,280	0.51	16,334	3,738	1.06	3,521
Transition probability from mild to moderate disease	7,584	0.72	10,483	2,361	1.49	1,585

Transition probability from moderate disease to compensatd cirrhosis	7,226	0.82	8,762	1,654	1.69	978
Cost of SVR state = £0	7,830	0.67	11,700	2,849	1.38	2,060
Reduce cost of PEG 2b by 20%	6,340	0.67	9,473	1,428	1.38	1,033
Reduce cost of PEG 2b by 30%	5,560	0.67	8,307	648	1.38	468
Reduce cost of RBV by 20%	7,246	0.67	10,827	2,334	1.38	1,688
Reduce cost of RBV by 30%	6,918	0.67	10,337	2,006	1.38	1,451

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 + 4 is associated with increased QALYs (with a range from 0.1 to 1.41 QALYs), but also increased costs (ranging from £4,260 to £10,560) in all simulations when compared with BSC (see Table 79 and Figure 21). Treatment for patients with genotypes 2 + 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).

Table 79 Mean costs and outcomes (percentile-based 95% confidence intervals) for HCV/HIV co-infected patients using peginterferon α-2b and ribavirin combination therapy, from probabilistic sensitivity analysis

Genotype		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	7,910 (5,593 to 9,673)	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	3,095 (-1,241 to 6,340)	1.36 (0.69 to 2.01)

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

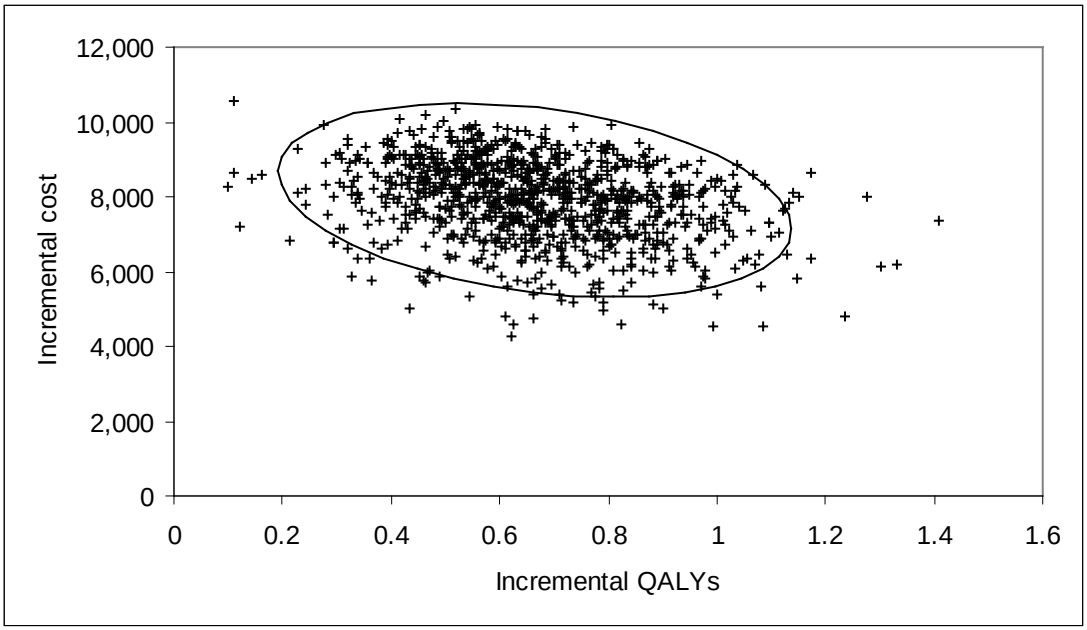
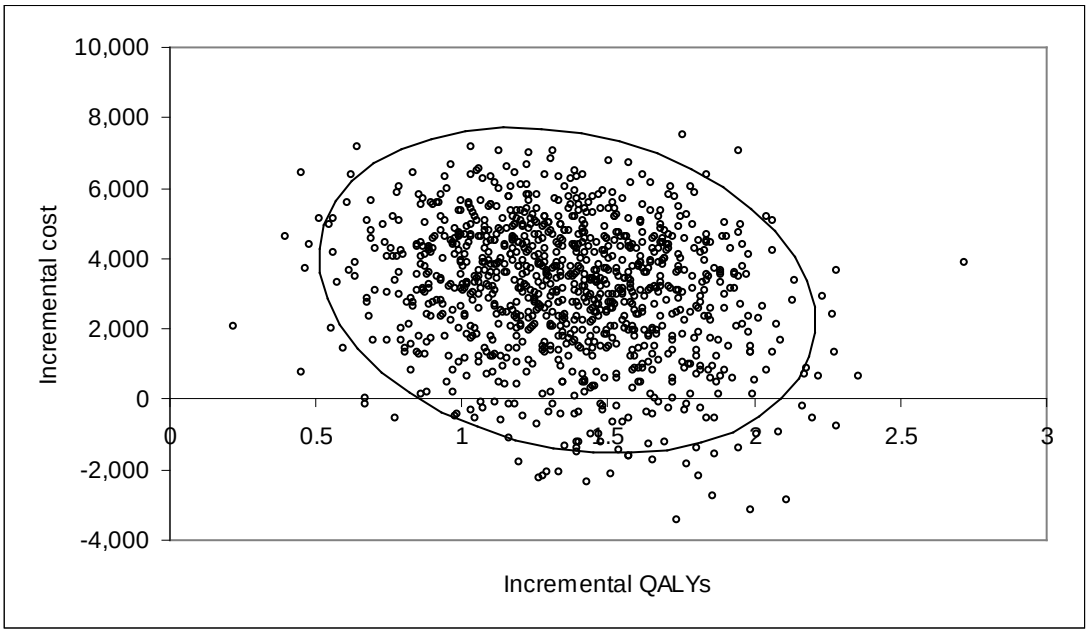


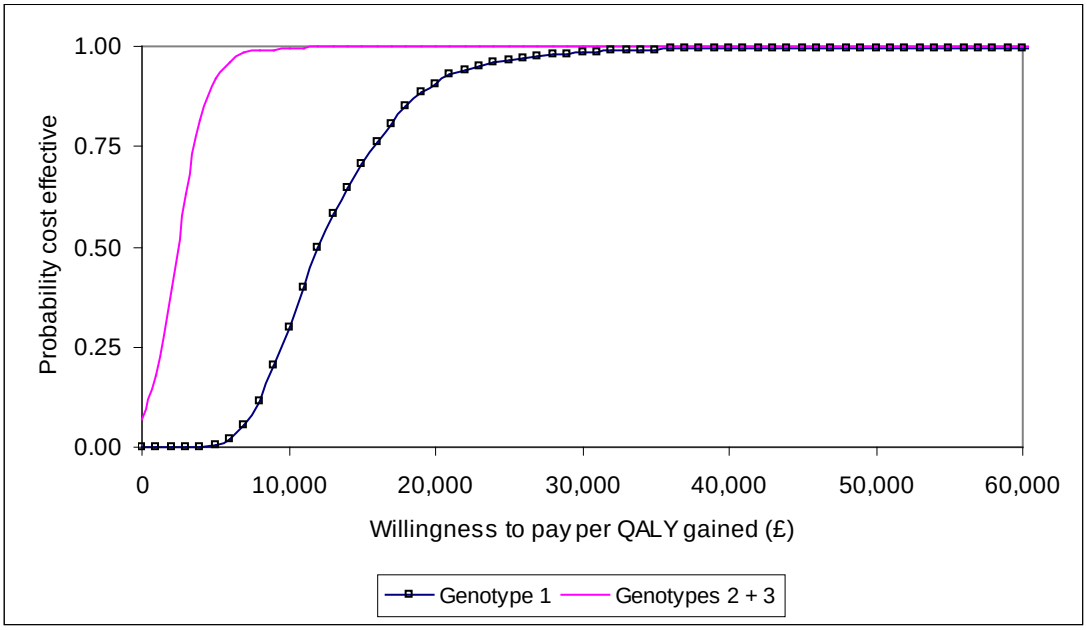
Figure 22 Cost-effectiveness plane for genotypes 2 + 3 - incremental cost and incremental QALYs for treatment of HCV/HIV co-infected patients with peginterferon α-2b and ribavirin combination therapy



In this analysis, treatment using peginterferon α-2b and ribavirin combination therapy for patients with genotypes 2 + 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 + 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.

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



5.5 Summary of key results

Systematic review of published cost-effectiveness and quality of life 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 anti-viral treatment strategies for patients who were co-infected with HCV and HIV. One of the evaluations[64] based their analysis on data from trials which included only patients mono-infected with HCV, while the other[65] used data from trials including co-infected patients. Both evaluations indicated that HCV anti-viral 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 system
- A systematic search for published studies of HRQoL found no relevant studies.

Roche submission to NICE

- Roche submitted a dossier in support of pegylated interferon α-2a combined with ribavirin in three sub-groups 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 sub-group analyses. A number of the clinical-effectiveness studies included used by the manufacturer do not make the comparisons specified by NICE (patients who did not respond[87] or relapsed[88] 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 for NICE TA106.[17] 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. Since both costs and outcomes are lower with shortened treatment duration, the ICERs are positive (in the south-east quadrant of the cost-effectiveness plane) - £15,472 for genotype 1 & 4 patients and £2,719 for genotype 2 & 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 anti-viral treatment does not fully offset treatment costs - resulting in positive ICERs (in the north-west 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 the APRICOT trial,[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 £1,765 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 probabilistic sensitivity analyses. 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;
    - the distribution of patients across stages of progressive liver disease;
    - the 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 in support of peginterferon α-2b combined with ribavirin in two of the three sub-groups 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 multi-centre, non-randomised open label uncontrolled study (for re-treatment in non-responding or relapsing patients) and a phase III open-label trial[93] (for patients with HCV/HIV co-infection). As the included studies do not make the comparisons specified by NICE (anti-viral 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{10654} 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).
- No systematic searches for health state utilities or costs are reported. The manufacturers did not report a critical appraisal of the EPIC3, Scotto and colleagues[95] or Laguno and colleagues 2004[93] 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.
- Two groups of patients were modelled in the Schering-Plough submission: the first of these was re-treated and relapsed patients, each based upon data from the EPIC3[94] clinical study report. In the group of 'non-responders' overall in the Schering-Plough submission, PEG + RBV cost £26,666, with a QALY gain of 1.04 over no treatment, resulting in an ICER of £4,387 per QALY gained. In genotypes 1 and 4 these results were £27,125, with a 0.7 QALY gain and an ICER of £7,177 per QALY gained. In 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 were patients co-infected with HCV/HIV, and modelled using effectiveness data from the Laguno and colleagues trial.[93] In this group overall , PEG +RBV cost £26,997, with a QALY gain of 2.32, which resulted in an ICER of £1,077. For genotypes 1 and 4 in this group, PEG +RBV cost £27,790, with

a QALY gain of 2.01, giving an ICER OF £1,637; 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 deterministic sensitivity analysis 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 when data from the Scotto and colleagues 2008[95] study were substituted for the EPIC trial. Where discounting was removed the ICER reduced to £1,265 per QALY gained in the re-treatment group. In the HCV/HIV co-infection group, PEG + RBV 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 sub-groups. The PSA reports high probabilities (over 90%) of treatment with peginterferon α-2b being cost effective at 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 anti-viral

treatment for chronic HCV. The model has a cycle length of one 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.
- SVRs 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 anti-viral 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 genotype 2+3 combined).
    - Shorter duration of treatment (from 48 to 24 weeks) with peginterferon α-2a for the sub-group 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 (since both incremental cost and incremental QALYs are negative) and range from around £34,000 per incremental QALY to £65,000 per incremental QALY. Since 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 α-2a for genotype 2 and 3 patients reduced total costs by approximately a quarter, and was associated with better outcome in the included trials. In these scenarios shortened treatment duration for the sub-group of genotype 2 or 3 patients with low baseline viral load and who achieve an RVR dominated standard duration.
    - Shorter duration of treatment (from 48 to 24 weeks) with peginterferon α-2b for the sub-group of genotype 1 patients with baseline LVL and who achieve an RVR was

associated with a reduction in costs of approximately £9,000. Combined with a QALY gain increase of 0.49, this resulted in peginterferon α-2b dominating the standard 48 week duration of treatment.

- None of the RCTs that examined re-treatment of patients previously treated with peginterferon, or that assessed peginterferon treatment in patients with HCV/HIV co-infection, identified by our searches met the inclusion criteria. The analyses of these patient sub-groups 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 α-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 by 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% (£3,398) in genotype 1 patients, and by approximately 5% (£1,415) 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 £9,169 per QALY gained in genotype 1 and £2,294 per QALY gained in genotype non-1.
- SVRs for the re-treated patients receiving peginterferon α-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 £9,380, 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 α-2b dominating BSC.
- Where an early stopping rule is applied for patients not demonstrating an EVR in genotypes 1 and 4, the incremental costs reduces to £3,256 and the QALY gain increases to 0.42, resulting in an ICER of £7,681. In genotypes 2 and 3 the incremental costs are reduced further, to -£2,850, the QALY gain increased slightly.
- For patients that are co-infected with HCV/HIV, treatment with peginterferon α-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% (£5,932) in genotypes 1 and 4 which resulted in a positive ICER of £7,941 per QALY gained in this group. Costs decreased overall as a result of treating genotypes 2 and 3 by approximately 8%, a reduction of £1,717. This resulted in peginterferon α-2a dominating BSC in this group of patients.

- For patients that are co-infected with HCV/HIV, treatment with peginterferon α-2b resulted in increased costs for both genotypes 1 and 4 and genotypes 2 and 3 (of £7,901 and £2,989 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 £11,806 per QALY gained, and in genotypes 2 and 3 this was £2,161 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 8) and, while 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 has been taken from comparatively small trials (20 to 40 patients per arm) that were not adequately powered to detect differences in SVR, or were derived from sub-groups 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 while 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 multi-national 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.[101] 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 sub-groups of patients covered by this review. The clinical audit data pre-dates NICE guidance on the use 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 remain relevant to modelling response to treatment where cirrhotic patients 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{6359}[17] 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.{366, 10654} Where evidence suggests that differential progression rates should be applied for the sub-groups 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 multi-centre trial and observational study,{10654, 6359} 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-naïve 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 quality of life weights are to some of the sub-groups of patients in the current assessment – re-treated patients are likely to be older while quality of life 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,{10654, 6359} 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. 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 anti-viral treatment in this group of patients was addressed in a sensitivity analysis.

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. Whilst 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 low 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 license criteria received shortened courses of anti-viral treatment, 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 and so have 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 anti-HCV infections need to be augmented by appropriate methods of referral to specialist care for further investigation and, if appropriate, anti-viral 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.

7 DISCUSSION

7.1 Statement of principle findings

7.1.1 Clinical-effectiveness

The results of six RCTs were included in this systematic review, all in patients 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 genotype 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), whilst 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 sub-group of those with LVL who attained an RVR (i.e. the patient sub-group meeting the licensed criteria for receiving shortened courses of therapy, and thus within the scope of the NICE appraisal). Note though, that this sub-group comprised 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 were powered for this sub-group 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. 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 the trials reported SVR as the primary outcome measure. The evidence showed that in the sub-group 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 genotype 2/3. 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 which increase the chance of response. (e.g. LVL and RVR, generally mild to moderate HCV-related liver damage, absence of significant co-morbidities or co-infections, absence of drug or alcohol abuse).

The evidence does suggest that patients in this sub-group 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 once 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 sub-groups (of varying sizes) of the randomised patients and are likely to be underpowered. The results of the trials in these sub-groups 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 to 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 sub-group 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 sub-groups 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 Section 4.1.1, no RCTs in patients co-infected with HCV/HIV comparing peginterferon alfa to 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 which peginterferon alfa is compared against 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 only eligible for inclusion in this review 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.

7.1.2 Cost-effectiveness

Systematic review of existing cost-effectiveness evidence

A systematic search of the literature for published economic evaluations that were relevant to 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 their analysis on data from clinical trials including HCV/HIV co-infected patients. Both evaluations were conducted in the context of the US health 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 in support of peginterferon α-2a combined with ribavirin in three sub-groups 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 sub-groups, using data from different clinical trials;
- treatment of patients with HCV/HIV co-infection

Schering-Plough submitted a dossier in support of peginterferon α-2b combined with ribavirin in two sub-groups 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 likely to over-estimate 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

Shorter treatment duration resulted in substantial reductions in anti-viral treatment costs (49% lower for genotype 1 + 4 patients and 31% lower for genotype 2 + 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. Since both costs and outcomes are lower with shortened treatment duration the ICERs are positive (in the south-east quadrant of the cost-effectiveness plane) - £15,472 for genotype 1 + 4 patients and £2,719 for genotype 2 + 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 £6,000. This arises from a high SVR observed in one trial that 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-west quadrant of the cost-effectiveness plane) - £3,334 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 which 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 trial.[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 £1,765, for peginterferon compared with best supportive care, 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 deterministic sensitivity analysis reported in the MS. Probabilistic sensitivity analyses 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

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 £4,536, resulting in an ICER of £4,387. These results were reported for a combined cohort of genotype 1 + 4 (84% of total) and genotype 2 + 3 patients. Separate results are also reported for the two genotype sub-groups: the ICERs were £7,177 per QALY gained for genotype 1 + 4 patients and £783 per QALY gained for genotypes 2 + 3 patients.

The submission also reports sub-group analyses (not stratified by genotype) for non-responding and relapsed patients separately – suggesting the QALY gain is higher for relapsed than for non-responding patients. Effectiveness data for this group of patients was taken from the unpublished EPIC study, 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 EPIC 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 £2,502, resulting in an ICER of £1,077. For patients with genotypes 1 + 4 the ICER was estimated at £1,637 per QALY gained, while for patients with genotypes 2 + 3 the ICER was £403 per QALY gained.

The deterministic sensitivity analysis 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 since dosing of both peginterferon α-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 sub-groups. The PSA reports high probability (over 90%) of treatment with peginterferon α-2b being cost effective for all analyses, at willingness to pay threshold 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 one 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. The proportion of men in the baseline cohort was based on our previous assessment.

For the sub-group of genotype 1 patients with baseline LVL and who achieve an RVR, shorter duration of treatment with peginterferon α-2a (from 48 to 24 weeks) reduced total costs by approximately one third (approximately £5,000), 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 (since both incremental cost and incremental QALYs are negative) and range from around £35,000 per incremental QALY to £65,000 per incremental QALY. Since 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 α-2a (from 24 to 16 weeks) for genotype 2 and 3 patients reduced total costs by approximately a quarter (between £2,000 and £3,000), 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 for the sub-group of genotype 2 or 3 patients with baseline LVL and who achieve an RVR dominated standard care.

For genotype 1 patients with baseline LVL and who achieve an RVR, shorter duration of treatment with peginterferon α-2b (from 48 to 24 weeks) reduced total costs by approximately one third (approximately £9,000), 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 α-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 sub-groups have used data that have not been formally quality-assessed in the same way as for the review of shortened treatment duration.

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

provided further detail on the trial reported by Jensen and colleagues.[87] In this analysis re-treatment using peginterferon α-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 due to adverse. Adopting an early stopping rule based on EVR lead to substantial reduction in incremental costs for treated patients. The ICERs for each group reduced to £9,169 per QALY gained in genotype 1 and £2,294 per QALY gained in genotype non-1.

For peginterferon α-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 reporting evidence form the EPIC3 study.[94] In this analysis re-treating patients with genotypes 1 and 4 increased costs by £9,380, 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 α-2b dominating BSC. Adopting an early stopping rule based on EVR lead to substantial reduction in incremental costs for treated patients. The ICERs for the group including genotypes 1 and 4 patients reduced to £7,681 per QALY gained.

For patients that are co-infected with HCV/HIV, treatment with peginterferon α-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% (£5,932) in genotypes 1 and 4 which resulted in a positive ICER of £7,941 per QALY gained in this group. Costs decreased overall as a result of treating genotypes 2 and 3 by approximately 8%, a reduction of £1,717. This resulted in peginterferon α-2a dominating BSC in this group of patients.

For patients that are co-infected with HCV/HIV, treatment with peginterferon α-2b resulted in increased costs for both genotypes 1 and 4 and genotypes 2 and 3 (of £7,901 and £2,989 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 £11,806 per QALY gained, and in genotypes 2 and 3 this was £2,161 per QALY gained.

7.2 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 which defined the research question, inclusion criteria, quality criteria, data extraction process and methods to be employed at different stages of the review (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 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 sub-groups as opposed to all randomised patients. It is unlikely that the RCTs were statistically powered in respect of these sub-groups 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 α-2a specifies that ribavirin should be given in a fixed dose of 800mg in 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 sub-groups 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 are to patients 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 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 α-2a and 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 α-2a or 2b in both of its arms, as opposed to the other RCTs each of which evaluated either 2a or 2b but not both in the same trial.

7.3 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 IU/ml to <615 IU/ml. Similarly, the threshold for LVL differed between trials with a cut-off HCV RNA level of <400,000 IU/ml 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.

SVR 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 address this by including sensitivity analyses adopting a lower probability of SVR in cirrhotic patients.

Quality of life/health state utility weights in the model were taken from reports on a multi-centre trial which recruited treatment-naïve 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 quality of life weights are to some of the sub-groups of patients in the current assessment – re-treated patients are likely to be older while quality of life 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,{10654, 6359} whilst 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 anti-viral 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 sub-groups and have used baseline characteristics from our previous assessment and a small audit undertaken in a London teaching hospital. Clinical experts fort his review regarded these assumptions as reasonable, but this remains an assumption and is not supported by robust evidence

8 CONCLUSIONS

8.1 Implications for service provision

A recommendation to extend anti-viral 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 of a patient's care is to be avoided and a more holistic approach adopted.

8.2 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 Phase 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 niave and treatment experienced patients, such as elaprevir 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 administred via injection every two 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 health service on their use.

9 REFERENCES

1. Thomson BJ, Finch RG. Hepatitis C virus infection. *Clin Microbiol Infect* 2005;**11**:86-94.

2. Flamm SL. Chronic hepatitis C virus infection. *JAMA* 2003;**289**:2413-7.

3. Health Protection Agency. *Hepatitis C in the UK: 2008 report.* London: Health Protection Agency Centre for Infections; 2008.

4. Booth J, O'Grady J, Neuberger J, on behalf of the Royal College of Physicians of London and the British Society of Gastroenterology. Clinical guidelines on the management of hepatitis C. *Gut* 2001;**49**:i1-i21.

5. Hoofnagle JH. Hepatitis C: the clinical spectrum of disease. *Hepatology* 1997;**26**:15S-20S.

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

7. Giraudon I, Ruf M, Maguire H, Charlett A, Ncube F, Turner J *et al*. Increase in diagnosed newly acquired hepatitis C in HIV-positive men who have sex with men across London and Brighton, 2002-2006: is this an outbreak? *Sexually Transmitted Infections* 2008;**84**:111-5.

8. The Global Burden Of Hepatitis. Global burden of disease (GBD) for hepatitis C. *J Clin Pharmacol* 2004;**44**:20-9.

9. Health Protection Agency, Health Protection Scotland, National Public Health Service for Wales, Communicable Disease Surveillance Centre Northern Ireland, Centre for Research on Drugs & Health Behaviour, London School of Hygiene & Tropical Medicine. *Shooting up: Infections among injecting drug users in the United Kingdom 2006*. London: Health Protection Agency; 2007.

10. Mohsen A, Easterbrook P, Taylor C, Norris S. Hepatitis C and HIV-1 coinfection. *Gut* 2002;**51**:601-8.

11. Pol S, Soriano V. Management of chronic hepatitis C virus infection in HIV-infected patients. *Clin Infect Dis* 2008;**47**:94-101.

12. Thomson EC, Main J. Epidemiology of hepatitis C virus infection in HIV-infected individuals. *J Viral Hepat* 2008;**15**:773-81.

13. Desmet VJ. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *J Hepatol* 2003;**38**:382-6.

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

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

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

17. Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess* 2007;**11**:1-205.

18. Sweeting MJ, De Angelis D, Neal KR, Ramsay ME, Irving WL, Wright M *et al*. Estimated progression rates in three United Kingdom hepatitis C cohorts differed according to method of recruitment. *J Clin Epidem* 2006;**59**:144-52.

19. Alberti A, Vario A, Ferrari A, Pistis R. Review article: chronic hepatitis C-natural history and cofactors. *Aliment Pharmacol Ther* 2005;**22**:74-8.

20. Sweeting MJ, De AD, Brant LJ, Harris HE, Mann AG, Ramsay ME. The burden of hepatitis C in England. *J Viral Hepat* 2007;**14**:570-6.

21. Di Bisceglie AM. Hepatitis C. *Lancet* 1998;**351**:351-5.

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

23. Martinez-Sierra C, Arizcorreta A, Diaz F, Roldan R, Martin-Herrera L, Perez-Guzman E *et al*. Progression of chronic hepatitis C to liver fibrosis and cirrhosis in patients coinfected with hepatitis C virus and human immunodeficiency virus. *Clin Infect Dis* 2003;**36**:491-8.

24. Martin-Carbonero L, Benhamou Y, Puoti M, Berenguer J, Mallolas J, Quereda C *et al*. Incidence and predictors of severe liver fibrosis in human immunodeficiency virus-infected patients with chronic hepatitis C: a European collaborative study. *Clin Infect Dis* 2004;**38**:128-33.

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

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

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

28. Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS* 2008;**22**:1979-91.

29. The Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet* 2008;**372**:293-9.

30. Macias J, Melguizo I, Fernandez-Rivera FJ, Garcia-Garcia A, Mira JA, Ramos AJ *et al*. Mortality due to liver failure and impact on survival of hepatitis virus infections in HIV-infected patients receiving potent antiretroviral therapy. *Eur J Clin Microbiol Infect Dis* 2002;**21**:775-81.

31. Mocroft A, Soriano V, Rockstroh J, Reiss P, Kirk O, De WS *et al*. Is there evidence for an increase in the death rate from liver-related disease in patients with HIV? *AIDS* 2005;**19**:2117-25.

32. Scottish Intercollegiate Guidelines Network (SIGN). *Management of Hepatitis C: a National Clinical Guideline (92)*. Edinburgh: Scottish Intercollegiate Guidelines Network; 2006.

33. National Institute for Health and Clinical Excellence. Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. *Technology Appraisal Guidance No 106* 2006.

34. Veldt BJ, Saracco G, Boyer N, Camma C, Bellobuono A, Hopf U *et al*. Long term clinical outcome of chronic hepatitis C patients with sustained virological response to interferon monotherapy. *Gut* 2004;**53**:1504-8.

35. Chander G, Sulkowski MS, Jenckes MW, Torbenson MS, Herlong HF, Bass EB *et al*. Treatment of chronic hepatitis C: a systematic review. *Hepatology* 2002;**36**:S135-S144.

36. Yoshida H, Arakawa Y, Sata M, Nishiguchi S, Yano M, Fujiyama S *et al*. Interferon therapy prolonged life expectancy among chronic hepatitis C patients. *Gastroenterol* 2002;**123**:483-91.

37. Gluud C, Brok J, Gong Y, Koretz RL. Hepatology may have problems with putative surrogate outcome measures. *J Hepatol* 2007;**46**:734-42.

38. National Institute for Clinical Excellence. Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C. *Technology Appraisal Guidance No 75*, 2004.

39. Davis GL. Monitoring of viral levels during therapy of hepatitis C. *Hepatology* 2002;**36**:S145-S151.

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

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

42. Roche UK. Summary of Product Characteristics - Peginterferon alfa-2a (Pegasys). Electronic Medicines Compendium 2009. *http://emc.medicines.org.uk/medicine/10081/SPC/Pegasys+135mcg+and+180mcg++solution+for+injection+in+Pre-filled+Syringe/* (accessed 18 May 2009)

43. Schering-Plough. Summary of Product Characteristics - Peginterferon alfa-2b (ViraferonPeg). Electronic Medicines Compendium 2009. *http://emc.medicines.org.uk/medicine/10321/SPC/ViraferonPeg+Pen+50%2c+80%2c+100%2c+120+or+150+micrograms++powder+and+solvent+for+solution+for+injection+in+pre-filled+pen/* (accessed 18 May 2009)

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

45. Rockstroh JK, Bhagani S, Benhamou Y, Bruno R, Mauss S, Peters L *et al*. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. *HIV Med* 2008;**9**:82-8.

46. Nelson M, Matthews G, Brook MG, Main J, Bateman P, Gilson R *et al*. BHIVA guidelines on HIV and chronic hepatitis: Coinfection with HIV and hepatitis C virus infection (2005). *HIV Med* 2005;**6**:96-106.

47. Joint Formulary Committee. *British National Formulary*. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 9 A.D. No. 58

48. Hartwell D, Shepherd J. Pegylated and non-pegylated interferon-alfa and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and meta-analysis. *Int J Technol Assess in Health Care* 2009;**25**:56-62.

49. Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care*. York Publishing Services Ltd.: CRD; 2009. Third edition

50. Zhao S, Cheng D, Liu E, Yu H, Yang H, Xue X *et al*. Peginterferon vs. interferon in the treatment of different HCV genotype infections in HIV patients. *Eur J Clin Microbiol Infect Dis* 2008;**27**:1183-92.

51. Kim AI, Dorn A, Bouajram R, Saab S. The treatment of chronic hepatitis C in HIV-infected patients: a meta-analysis. *HIV Med* 2007;**8**:312-21.

52. Mangia A, Minerva N, Bacca D, Cozzolongo R, Ricci GL, Carretta V *et al*. Individualized treatment duration for hepatitis C genotype 1 patients: A randomized controlled trial. *Hepatology* 2008;**47**:43-50.

53. Liu C-H, Liu C-J, Lin C, Liang C-C, Hsu S-J, Yang S-S *et al*. Pegylated interferon-alpha-2a plus ribavirin for treatment-naive Asian patients with hepatitis C virus genotype 1 infection: A multicenter, randomized controlled trial. *Clin Infect Dis* 2008;**47**:1260-9.

54. Yu ML, Dai CY, Huang JF, Chiu CF, Yang YH, Hou NJ *et al*. Rapid virological response and treatment duration for chronic hepatitis C genotype 1 patients: a randomized trial. *Hepatology* 2008;**47**:1884-93.

55. Yu ML, Dai CY, Huang JF, Hou NJ, Lee LP, Hsieh MY *et al*. A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. *Gut* 2007;**56**:553-9.

56. von Wagner M, Huber M, Berg T, Hinrichsen H, Rasenack J, Heintges T *et al*. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. *Gastroenterol* 2005;**129**:522-7.

57. Liu CH, Liu CJ, Lin CL, Liang CC, Hsu SJ, Yang SS *et al*. A Randomized Trial of 24-Versus 48-Week Peginterferon Alfa-2A Plus Ribavirin for Treatment-Naive Taiwanese Patients with Hepatitis C Virus Genotype 1 Infection. *Hepatology* 2008;**48**:320A.

58. Yu M, Dai C, Huang J, Lee L, Hsieh M, Chiu C *et al*. High chance of cure in HCV genotype 1 patients with a low viral load achieving an RVR treated for 24 wks with peginterferon alfa-2a (PEGASYS®) plus ribavirin (COPEGUS®): Prospective, randomized, controlled study comparing 24 and 48 weeks of treatment. *Hepatology* 2007;**46**:822A-3A.

59. Berg T, Weich V, Teuber G, Klinker H, Moller B, Rasenack J *et al*. Individualized treatment strategy according to early viral kinetics in hepatitis C virus type 1-infected patients. *Hepatology* 2009;**50**:369-77.

60. Younossi ZM, Nader FH, Bai C, Sjogren R, Ong JP, Collantes R *et al*. A phase II dose finding study of darbepoetin alpha and filgrastim for the management of anaemia and neutropenia in chronic hepatitis C treatment. *J Viral Hepat* 2008;**15**:370-8.

61. National Institute for Health and Clinical Excellence. Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C (Part-review of TA75 and TA106): final scope. http://www.nice.org.uk/guidance/index.jsp?action=download&o=44230 May/2009.

62. Roche UK. Summary of Product Characteristics - Ribavirin (Copegus). Electronic Medicines Compendium 2009. *http://emc.medicines.org.uk/medicine/11755/SPC/Copegus+200mg/* (accessed 18 May 2009)

63. Nguyen-Khac E, Capron D, Castelain S, Francois C, Braillon A. Personalized therapy for chronic viral hepatitis C in the naive patient: How can we optimize treatment duration as a function of viral genotype? *Eur J Inter Med* 2007;**18**:510-5.

64. Kuehne FC, Bethe U, Freedberg K, Goldie SJ. Treatment for hepatitis C virus in human immunodeficiency virus-infected patients: clinical benefits and cost-effectiveness. *Arch Intern Med* 2002;**162**:-56, 2002.

65. Campos NG, Salomon JA, Servoss JC, Nunes DP, Samet JH, Freedberg KA *et al*. Cost-effectiveness of treatment for hepatitis C in an urban cohort co-infected with HIV. *Am J Med* 2007;**120**:272-9.

66. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A *et al*. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004;**351**:438-50.

67. Drummond MF, Sculpher MJ, O'Brien BJ, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. Oxford: Oxford University Press; 2005

68. National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf . 2008.

69. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R *et al*. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;**8**:1-158.

70. Soto B, Sanchez-Quijano A, Rodrigo L. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol* 1997;**26**:1-5.

71. Di Martino V, Rufat P, Boyer N. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long term retrospective cohort study. *Hepatology* 2001;**34**:1193-9.

72. Schackman, B. R., Goldie, S. J., Freedberg, K. A., Losina, E, Brazier, J., and Weinstein, M. C. Comparison of health state utilities using community and patient preference weights derived from a survey of patients with HIV/AIDS. *Med Decis Making* 2002; **22**:27-38.

73. Bozzette, S., Berry, SH, Duan, N, and et al for the HIV Cost and Services Utilization Study Consortium. The care of HIV-infected adults in the United States. *N Engl J Med* 1998; **339**:1897-1904.

74. Multi-attribute utility function for a comprehensive health status classification system: Health Utilities Index Mark 2. *Med Care* 1996;**34**:702-722.

75. Brazier, J., Usherwood, T, Harper, R, and Thomas, K. Deriving a preference-based single index from the UK SF-36 Health Survey. 1998;**51**:1115-1128.

76. Bennett WG, Inoue Y, Beck JR, Wong JB, Pauker SG, Davis GL. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. *Ann Intern Med* 1997;**127**:855-65.

77. Davis GL, Beck JR, Farrell G, Poynard T. Prolonged treatment with interferon in patients with histologically mild chronic hepatitis C: a decision analysis. *J Viral Hepat* 1998;**5**:313-21.

78. Wong JB, Koff RS. Watchful waiting with periodic liver biopsy versus immediate empirical therapy for histologically mild chronic hepatitis C. A cost-effectiveness analysis. *Ann Intern Med* 2000;**133**:665-75.

79. Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Cost-effectiveness of Treatment for Chronic Hepatitis C Infection in an Evolving Patient Population. *JAMA* 2003;**290**:228-37.

80. Grieve R, Roberts J. Economic evaluation for hepatitis C. *Acta Gastroenterol Belg* 2002;**65**:-9, 2002.

81. Grieve R, Roberts J, Wright M, Sweeting M, Deagelis D, Rosenberg W *et al*. Cost-effectiveness of interferon {alpha} or peginterferon {alpha} with ribavirin for histologically mild chronic hepatitis C. *Gut* 2006;**55**:1332-8.

82. Wright M, Grieve R, Roberts J, Main J, Thomas HC, UK Mild Hepatitis C Trial Investigators. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess* 2006;**10**:1-113.

83. Kind P, Hardman G, Macran S. *UK Population norms for EQ-5D. CHE Discussion Paper 172*. York: Centre for Health Economics, York University; 1999.

84. Dolan P, Gudex C, Kind P, Williams A. *A social tariff for EuroQol: results from a UK general population survey*. Centre for Health Economics. Discussion Paper 138. York: CHE, University of York; 1995.

85. Curtis L. *Unit Costs of Health and Social Care*. Canterbury: Personal Social Services Research Unit, University of Kent; 2008

86. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost effectiveness analysis. *Medical Decision Making* 2009;**18**:S68-S80.

87. Jensen DM, Marcellin P, Freilich B, Andreone P, Di BA, Brandao-Mello CE *et al*. Re-treatment of patients with chronic hepatitis C who do not respond to peginterferon-alpha2b: a randomized trial. *Ann Intern Med* 2009;**150**:528-40.

88. Berg C, Goncales FL, Jr., Bernstein DE, Sette H, Jr., Rasenack J, Diago M *et al*. Re-treatment of chronic hepatitis C patients after relapse: efficacy of peginterferon-alpha-2a (40 kDa) and ribavirin. *J Viral Hepat* 2006;**13**:435-40.

89. Shiffman ML, Suter F, Bacon BR, Nelson D, Harley H, Sola R *et al*. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2007;**357**:124-34.

90. Hadziyannis SJ, Sette H, Jr., Morgan TR, Balan V, Diago M, Marcellin P *et al*. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;**140**:346-55.

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

92. Laguno M, Cifuentes C, Murillas J, Veloso S, Larrousse M, Payeras A *et al*. Randomized trial comparing pegylated interferon alpha-2b versus pegylated interferon alpha-2a, both plus ribavirin, to treat chronic hepatitis C in human immunodeficiency virus patients. *Hepatology* 2009;**49**:22-31.

93. Laguno M, Murillas J, Blanco JL, Martinez E, Miquel R, Sanchez-Tapias JM *et al*. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. *AIDS* 2004;**18**:F27-F36.

94. Poynard T, Schiff E, Terg R, Moreno Otero R, Flamm S, Schmidt W *et al.* Sustained viral response (SVR) is dependent on baseline characteristics in the re-treatment of previous alfa interferon/ribavirin (I/R) nonresponders (NR): Final results from the EPIC3 program. 43rd Annual Meeting of the European Association for the Study of the Liver (EASL), Milan, Italy; April 23rd - 27th, 2008.

95. Scotto G, Fazio V, Fornabaio C, Tartaglia A, Di TR, Saracino A *et al*. Peg-interferon alpha-2a versus Peg-interferon alpha-2b in nonresponders with HCV active chronic hepatitis: a pilot study. *J Interferon Cytokine Res* 2008;**28**:623-9.

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

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

98. Sonnenberg FA, Gregory P, Yomtovian R, Russell LB, Tierney W, Kosmin M *et al*. The cost-effectiveness of autologous transfusion revisited: implications of an increased risk of bacterial infection with allogeneic transfusion. *Transfusion* 1999;**39**:808-7.

99. Boring CC, Squires TS, Tong T. Cancer statistics, 1993. *CA Cancer J Clin* 1993;**43**:7-26.

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

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

102. Siebert U, Sroczynski G, Rossol S, Wasem J, Ravens-Sieberer U, Kurth BM *et al*. Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C. *Gut* 2003;**52**:425-32.

103. Bennett WG, Inoue Y, Beck JR, Wong JB, Pauker SG, Davis GL. Estimates of the Cost-Effectiveness of a Single Course of Interferon-alpha2b in Patients with Histologically Mild Chronic Hepatitis C. *Ann Intern Med* 1997;**127**:855-65.

104. Roche. *Pegasys (Peginterferon alfa-2a) and Ribavirin for the treatment of chronic hepatitis C (Part review of TA75 and TA106).* NICE MTA Submission. 2009.

105. Schering-Plough Ltd. *Pegylated interferon alfa-2b and ribavirin for hepattis C: re-treatment of patients previously failing therapy and treatment of HIV/ HCV co-infected patients*. NICE MTA Submission. 2009.

106. Longworth L, Young T, Ratcliffe J, Bryan S, Buxton M. *Economic evaluation of the Transplantation Programme in England and Wales: An assessment of the costs of liver transplantation.* Unpublished Report to the Department of Health. 2001.

107. NHS Centre for Reviews and Dissemination. NHS economic evaluation database handbook. http://www.york.ac.uk/inst/crd/pdf/nhseed-handb07.pdf Apr./2007. (accessed 20 Aug. 2008)

108. Shiffman ML, Di Bisceglie AM, Lindsay KL, Morishima C, Wright EC, Everson GT *et al*. Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. *Gastroenterol* 2004;**126**:1015-23.

109. Everson GT, Hoefs JC, Seeff LB, Bonkovsky HL, Naishadham D, Shiffman ML *et al*. Impact of disease severity on outcome of antiviral therapy for chronic hepatitis C: Lessons from the HALT-C trial. *Hepatology* 2006;**44**:1675-84.

110. Shiffman ML, Mihas AA, Millwala F, Sterling RK, Luketic VA, Stravitz RT *et al*. Treatment of chronic hepatitis C virus in African Americans with genotypes 2 and 3. *Am J Gastroenterol* 2007;**102**:761-6.

111. Yoshida EM, Sherman M, Bain VG, Cooper CL, Deschenes M, Marotta PJ *et al*. Retreatment with Pegylated interferon alpha-2a and ribavirin in patients with chronic hepatitis C who have relapsed or not responded to a first course of peylated interferon-based therapy. *Can J Gastroenterol* 2009;**23**:180-4.

112. Parise ER, de Oliveira AC, Conceica~o RDO, Amaral AC, Leite K. Response to treatment with interferon-alpha and ribavirin in patients with chronic hepatitis C virus genotypes 2 and 3 depends on the degree of hepatic fibrosis. *Brazilian J Infect Dis* 2006;**10**:78-81.

113. Zeuzem S, Pawlotsky JM, Lukasiewicz E, von Wagner M, Goulis I, Lurie Y *et al*. International, multicenter, randomized, controlled study comparing dynamically individualized versus standard treatment in patients with chronic hepatitis C. *J Hepatol* 2005;**43**:250-7.

114. Jensen DM, Morgan TR, Marcellin P, Pockros PJ, Reddy KR, Hadziyannis SJ *et al*. Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. *Hepatology* 2006;**43**:954-60.

115. Ferenci P, Fried MW, Shiffman ML, Smith CI, Marinos G, Goncales FL, Jr. *et al*. Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2a (40 KD)/ribavirin. *J Hepatol* 2005;**43**:425-33.

116. Ferenci P, Laferl H, Scherzer TM, Gschwantler M, Maieron A, Brunner H *et al*. Peginterferon alfa-2a and ribavirin for 24 weeks in hepatitis C type 1 and 4 patients with rapid virological response. *Gastroenterol* 2008;**135**:451-8.

117. Carrat F, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, Benzekri A *et al*. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *JAMA* 2004;**292**:2839-48.

118. Pol S, Carrat F, Bani-Sadr F, Rosenthal E, Lunel F, Morand P *et al*. Final results of ANRS HC02-ribavic: A randomized controlled trial of pegylated-interferon alpha-2b plus ribavirin vs interferon alpha-2b plus ribavirin for naive HCV-HIV co- infected patients. *J Hepatol* 2005;**42**:10-1.

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

120. Fried MW, Hadziyannis SJ, Fried MW, Hadziyannis SJ. Treatment of chronic hepatitis C infection with peginterferons plus ribavirin. *Semin Liver Dis* 2004;**24**:47-54.

121. Crespo M, Sauleda S, Esteban JI, Juarez A, Ribera E, Andreu AL *et al*. Peginterferon alpha-2b plus ribavirin vs interferon alpha-2b plus ribavirin for chronic hepatitis C in HIV-coinfected patients. *J Viral Hepat* 2007;**14**:228-38.

122. Cargnel A, Angeli E, Mainini A, Gubertini G, Giorgi R, Schiavini M *et al*. Open, randomized, multicentre italian trial on PEG-IFN plus ribavirin versus PEG-IFN monotherapy for chronic hepatitis C in HIV-coinfected patients on HAART. *Antivir Ther* 2005;**10**:309-17.

10 APPENDICES

Appendix 1 Methods from research protocol

1. Title of the project:

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

5. 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]

5.1 Search strategy

A search strategy will be developed and tested by an experienced information scientist. The strategy will be designed to identify: (i) clinical-effectiveness studies reporting on comparisons between peginterferon and ribavirin combination therapy (or peginterferon monotherapy for those who cannot tolerate ribavirin) and BSC or standard-duration courses of peginterferon/ribavirin (as described in section 5.2); (ii) 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), the Cochrane Central Register of Controlled Trials, CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE), the NHS Economic Evaluation Database (NHS EED) and 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) & Conference Proceedings Citation Index - Science (CPCI) (ISI Web of Knowledge); Biosis Previews (ISI Web of Knowledge); NIHR-Clinical Research Network Portfolio; Clinical Trials.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 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 (NB. 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 re-screened 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.

5.2 Inclusion and exclusion criteria

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

5.2.1 Population

Adults with chronic 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 at the start of treatment and a rapid viral response (defined as HCV RNA undetectable by week 4);*
  - patients with genotype 1 with a low viral load 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).

5.2.2 Intervention

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

5.2.3 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/ribavirin combination therapy (up to 24 or 48 weeks as appropriate)

5.2.4 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. ALT levels)
- histological improvement (fibrosis and inflammation)
- survival
- adverse effects of treatment
- health-related quality of life
- cost-effectiveness (incremental cost per QALY)

5.2.5 Types of studies

- Fully published RCTs will be included.
- Studies published as abstracts or conference presentations from 2007 onwards will only be included 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.

5.3 Screening and data extraction process

5.3.1 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.

5.3.2 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.

5.4 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 (using principles outlined in the NHS EED Handbook[107]). 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 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.

5.5 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 allows, clinical- and cost-effectiveness will be assessed according to patient sub-groups (e.g. by genotype, baseline viral load).

6. Methods for synthesising evidence of cost-effectiveness

6.1 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.

6.2 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 SHTAC for a previous NICE assessment of treatment for mild chronic hepatitis C[96] will be reviewed to assess its applicability to the patient sub-groups 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 Personal Social Services. 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 sub-groups 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.

6.2.1 Methods for estimating quality of life

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' quality of life, 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]

6.2.2 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.

7. Handling the company submission(s)

All data submitted by the manufacturers will be considered if received by the TAR team no later than 27/08/09. 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 to 2009 (searches from the previous assessment reports[17,44] covered the period 2000 to 2007). The strategies were translated to search the other databases listed in Section 3.1.

Clinical-effectiveness searches

Medline (OVID)

1 (hepatitis c or HCV).mp. (35528)
2 exp Hepatitis C/ (26263)
3 Hepatitis C, Chronic/ (9982)
4 Hepacivirus/ (12474)
5 or/1-4 (35757)
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$) or ViraferonPeg or pegintron or Pegasys).mp. (15918)
9 Interferon Alfa-2a/ (2560)
10 Interferon Alfa-2b/ (3487)
11 Polyethylene Glycols/ (13117)
12 11 and (9 or 10) (1364)
13 6 or 7 or 8 or 12 (19230)
14 5 and 13 (4722)
15 limit 14 to (english language and humans and yr="2007 - 2009") (1144)
16 (systematic$ adj2 review$).mp. (18692)
17 (systematic$ adj2 overview$).mp. (354)
18 meta-analysis/ (18478)
19 (meta analysis or metaanalysis).ab,pt,ti. (25398)
20 randomized controlled trial.pt. (172423)
21 Randomized Controlled Trial/ (172423)
22 random allocation/ (29335)
23 random*.ti,ab. (310605)
24 controlled clinical trial.pt. (33195)
25 Controlled Clinical Trial/ (33195)
26 randomized controlled trials/ (51594)
27 Single-Blind Method/ (10146)
28 Double-Blind Method/ (55762)
29 ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw. (53879)
30 exp placebos/ (9753)
31 placebo*.ti,ab. (69682)
32 exp research design/ (154706)
33 or/16-32 (520197)
34 15 and 33 (233)
35 (letter or comment or editorial).pt. (551934)
36 34 not 35 (225)
37 from 36 keep 1-222 (222)

(222 in search on 20/05/09; re-ran for strategy on 02/06/09 - extra 3 results)

Added in interferon terms on 02/06/09

38 interferon alpha/ (8733)
39 (interferon alpha or interferon alfa or roferon or intron or viraferon).ti,ab. (27829)
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/ (13975)
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. (551934)
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. (40260)
2 exp Hepatitis C/ or exp Hepatitis C virus/ (37333)
3 1 or 2 (40260)
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. (25587)
7 exp Alpha Interferon/ (21113)
8 Recombinant Alpha2a Interferon/ (1749)
9 Recombinant Alpha2b Interferon/ (2660)
10 interferon/ or alpha2a interferon/ or alpha2b interferon/ or alpha interferon/ (36974)
11 or/4-10 (58971)
12 3 and 11 (12123)
13 limit 12 to (human and english language and yr="2007 - 2009") (2516)
14 (systematic$ adj2 review$).mp. (35802)
15 (systematic$ adj2 overview$).mp. (341)
16 (meta analy$ or metaanaly$).ti,ab,pt. (21234)
17 exp meta analysis/ (31882)
18 randomized controlled trial/ (139490)
19 controlled clinical trial/ (61251)
20 exp randomization/ (24841)
21 exp double blind procedure/ (53393)
22 exp single blind procedure/ (7234)
23 placebo*.tw. (70462)
24 random*.tw. (295710)
25 ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw. (55235)
26 ((hand or manual or computer or electronic or database) adj2 search*).ti,ab. (8649)
27 or/14-26 (410504)
28 13 and 27 (337)
29 (comment or editiorial or letter).pt. (305933)
30 28 not 29 (334)
31 from 30 keep 1-334 (334)

Cost-effectiveness searches

Medline (OVID)

1 ("hepatitis C" or HCV).mp. (35682)
2 exp hepatitis C/ or Hepatitis C, Chronic/ or exp Hepacivirus/ (29926)
3 or/1-2 (35914)
4 exp "Costs and Cost Analysis"/ (82109)
5 exp Cost-Benefit Analysis/ (30108)
6 exp health care costs/ (26090)
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/ (10228)
13 or/4-12 (102814)
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. (16012)
19 Interferon Alfa-2a/ (2577)
20 Interferon Alfa-2b/ (3506)
21 Polyethylene Glycols/ (13172)
22 21 and (19 or 20) (1379)
23 ((interferon adj1 alpha) or (interferon adj1 alfa)).ti,ab. (11238)
24 (roferon or intron or viraferon).ti,ab. (18563)
25 hepatitis c/dt (2820)
26 hepatitis c chronic/dt (4565)
27 or/16-18,22-26 (49445)
28 15 and 27 (29)

Embase (OVID)

1 (hepatitis C or hcv).mp. (40384)
2 exp Hepatitis C/ or exp Hepatitis C virus/ (37440)
3 1 or 2 (40384)
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. (25641)
7 exp Alpha Interferon/ (21178)
8 Recombinant Alpha2a Interferon/ (1751)
9 Recombinant Alpha2b Interferon/ (2663)
10 interferon/ or alpha2a interferon/ or alpha2b interferon/ or alpha interferon/ (37087)
11 or/4-10 (59136)
12 3 and 11 (12158)
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/ (30500)
20 economic evaluation/ (4615)

21 pharmacoeconomics/ (870)
22 budget/ (6833)
23 "resource use".ti,ab. (2058)
24 (cost or economic*).ti. (27489)
25 *health economics/ (2099)
26 *health care cost/ (7402)
27 or/13-26 (81064)
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. (489386)
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/ (10595)
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 utilit$ ind$).mp. (381)
32 ((multiattribute$ 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$.mp. (37389)
37 linear scal$.mp. (292)
38 linear analog$.mp. (349)
39 visual analog$.mp. (14997)
40 (categor$ adj2 scal$).mp. (595)
41 or/1-40 (81641)
42 (letter or editorial or comment).pt. (556056)
43 41 not 42 (79235)
44 (hepatitis C or hcv).mp. (35792)
45 exp Hepatitis C/ or Hepatitis C, Chronic/ or exp Hepacivirus/ (30013)
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. (19254)
49 ("hepatitis C" or HCV or "hepacivurs").ti. (22969)
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. (58665)
38 visual analog*.mp. (19195)
39 (categor* adj scale*).mp. (255)
40 linear scal*.mp. (214)
41 linear analog*.mp. (345)
42 or/1-41 (97590)
43 (editorial or letter or comment).pt. (491976)
44 42 not 43 (94514)
45 exp hepatitis C/ or exp hepacivirus/ (37643)
46 ("Hepatitis C" or HCV).mp. (40598)
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 Hep C submission to NICE 2009

Summary

- Manufacturer's submission 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" (page 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 sub-group analyses are included, some of which appear to have been funded by Roche (and published), and some which are 'data on file'.
- Of the 6 RCTs currently included in the SHTAC systematic review of clinical-effectiveness, only 2 have been included by Roche.

Re-treatment studies

Study included in manufacturer's submission	Eligible for inclusion in the current SHTAC systematic review of clinical-effectiveness?	Study details	Comments
MV17150 REPEAT study Jensen *et al*. (2009)[87]	No	• 942 patients treated, all non-responders to prior PEG • Four arm trial: peginterferon α-2a, 360 µg/wk, for 12 weeks, then 180 µg/wk to complete 72 weeks (group A) or 48 weeks (group B), or peginterferon α-2a, 180 µg/wk for 72 weeks (group C) or 48	• Active comparator study (different induction doses / lengths of PEG) • In the economic model SVRs are used from a sub-group of non responders from this study (data on file)

			weeks (group D).	
HALT-C (lead in phase)	Shiffman *et al.* (2004)[108]	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 *et al.* (2006)[109]	No	• Described as an updated publication data set used as part of the European Medicines Agency filing in Feb 2008 • Reports 1046 patients who had RNA assessments at wk 20 and 72. Analyses results in 4 sub-groups of patients subdivided by increasing liver disease severity	
	Shiffman *et al.* (2007)[110]	No	• Sub-group of 936 G1 patients with RNA assessments at wk 20 and 72. (a sub-group of the 1046 in Everson *et al.*)	
WV16143 Berg *et al*. (2006)[88]		No	• Described as a 'supporting study' • Uncontrolled trial in 64 patients. Patients had originally been in the NV15942 trial by Hadziyannis *et al*. but who had relapsed.	Uncontrolled
Yoshida *et al*. (2009)[111]		No	• Described as a 'supporting study' • Post-hoc analysis of a Canadian multicenter open-label study • 87 non-responders/relapsers.	
Parise *et al*. (2006)[112]		No	• Described as a 'supporting study' • 134 Brazillian relapsers / non-responders to non-PEG IFN / RBV	

Shorter courses studies: Genotypes 2 / 3

Study included in manufacturer's submission		**Eligible for inclusion in the current SHTAC systematic review of clinical-effectiveness?**	**Study details**	**Comments**
ACCELERATE NV17317	Shiffman *et al.*(2007)[89]	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 *et al.* (2005)[113]	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 wk arm, 200 patients with RVR and LVL in 24 wks arm.	• Attributes this retrospective analysis to Zeuzem at al 2005 (the Zeuzem reference on our database does not seem to resemble this study though (Ref ID 9525). • Manufacturer uses SVRs from this study in their economic model. (89% for 16 wk group vs 94% for 24 wk group) • These SVRs are similar to those used in the Von Wagner *et al.* and Yu *et al.* studies below
Von Wagner *et al.* (2005)[56]		Yes	• Both studies described as 'supportive' evidence in the submission. Mentions that both used unlicensed weight based RBV doses for G2 / 3 (hence why not included in their main analysis)	• Von Wagner *et al.* RBV dose = 800/1000/1200 mg • Yu *et al.* RBV dose = 1000/1200mg
Yu *et al.* (2007)[55]		Yes		

Shorter courses studies: Genotype 1

Study included in manufacturer's submission	Eligible for inclusion in the current SHTAC systematic review of clinical-effectiveness?	Details	Comments
Jensen *et al*. (2006)[114]	No	• Retrospective analysis based on the one third of G1 patients who achieved an SVR after 24 wks treatment in the Hadziyannis trial (2004) (incorrectly referred to as 2006 on page 97 of submission). • Purpose was to assess factors associated with RVR and an SVR in G1 pts treated for 24 wks.	• SVRs from this study are used in manufacturer's economic model.
Ferenci *et al*. (2005)[115]	No	• Retrospective analysis of data from an RCT of 48 wks PEG + RBV treatment in 1121 patients (compared to IFN + RBV).	

NB. There is no mention of Liu *et al*. or Yu *et al*.genotype 1 studies included in the SHTAC TAR.

Shorter courses studies: Genotype 4

Study included in manufacturer's submission	Eligible for inclusion in the current SHTAC systematic review of clinical-effectiveness?	Details	Comments
Ferenci *et al*. (2008)[116]	No	• Retrospective analysis of NV15801 (Jensen *et al*. 2006) and NV 15942 (Hadziyannis trial, 2004) • NB. on page 106 they refer to this as being a Research Report 1023045 data on file, and refer to the clinical trials as NV15801 (Fried	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 week 12 to 48 or 72

		et al .2002) and NV 15942 (Yu *et al*., 2008). There is some confusion here regarding the identity of the trials.	weeks. The journal paper only presents SVRs for the 24 weeks group anyway (on-going trial)

HIV & HCV co-infection

Study included in manufacturer's submission	Eligible for inclusion in the current SHTAC systematic review of clinical-effectiveness?	Details	Comments
APRICOT Torriani *et al*. (2004)[66]	No	• 868 treatment naïve co-infected patients randomised to receive: peginterferon α-2a (180 µg/week) plus ribavirin (800 mg per day); peginterferon α-2a plus placebo, or interferon α-2a (3 million IU three times a week) plus ribavirin	
Laguno *et al*. (2009)[92]	No	• Prospective multicentre RCT in Spain. Compares PEG α-2a with PEG α-2b	Described in the MS as a 'supporting study'

Schering-Plough Hep C submission to NICE 2009

- Manufacturer's submission only covers the re-treatment and HIV & HCV 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 manufacturer's submission	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 G1 and 4 EVR/SVR = 29.76% / 48.65; G2 and 3 = 79.13% and 69.95% respectively.	• Similar trial to HALT-C, but uses PEG 2B.
Scotto *et al*. (2008)[95]	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.

HIV & HCV co-infection

Study included in manufacturer's submission	Eligible for inclusion in the current SHTAC systematic review of clinical-effectiveness?	Details	Comments
P01017 (Carrat *et al*.2004)[117] (Pol *et al*. 2005)[118]	No No	• RCT PEG α-2b + RBV vs IFN + RBV	Active comparator studies, not within scope of appraisal
P02080 (Laguno *et al.* 2004)	No	• RCT PEG α-2b + RBV vs IFN + RBV • Efficacy estimates from this trial used in their economic evaluation. G1 and 4 = 38%; G2 and 3 = 53%	
Laguno *et al*. (2009)[92]	No	• RCT PEG α-2a + RBV vs PEG α-2b + RBV • Efficacy estimates from this trial used in sensitivity analysis	

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 peginterferon and ribavirin (or peginterferon monotherapy) • HIV & HCV co-infected • Eligible for shortened course of treatment NB. 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 peginterferon and ribavirin (or peginterferon monotherapy); and / or HIV & HCV co-infected) 1. Peginterferon + ribavirin 2. Peginterferon monotherapy Compared to BSC/placebo **Intervention:** (Patients eligible for shortened course of treatment): • genotype 2/3 patients with LVL and RVR, shorten tx from 24 to 16 wks (Peg 2a only) • genotype 1 patients with LVL and RVR, shorten tx from 48 to 24 wks (Peg 2a or 2b) • genotype 4 patients with RVR, shorten tx from 48 to 24 wks (Peg 2a only) 1. Peginterferon + ribavirin 2. Peginterferon monotherapy	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	EXCLUDE3 (E3) (not the appropriate intervention)

Compared to ‘standard’ duration courses of peginterferon/ribavirin (up to 24 or 48 weeks as appropriate)				
Outcomes: Sustained Viral Response (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 2a; ≤600,000 IU/ml Peg 2b); RVR, rapid virological response (HCV RNA undetectable at week 4 [genotype 2/3]; HCV RNA undetectable at week 4 and 24 [genotype 1/4])

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, e.g. 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 drop-outs 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 intention to treat 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 16/11/09		Reviewer 2: DH 16/11/09	
Reference and Design	**Intervention**	**Participants**	**Outcome measures**
Ref ID: [59] **Author:** Berg *et al*. **Year:** 2009 **Study design**: Open-label, multi-centre RCT **Number of centres:** 19 **Country**: Germany **Sponsor**: Essex Pharma (subsidiary of Schering-Plough), Bayer diagnostics, German competenc e network for Viral Hepatitis (German Ministry of Education and Research)	**Group 1: Standard treatment duration** n = 225 **Drug 1: PegIFN α-2b** *Dose*: 1.5 µg/kg/ week *Duration*: 48 weeks **Drug 2: Ribavirin** *Dose*: 800 -1,400 mg/d *Duration*: 48 weeks **Group 2: Variable treatment duration** n = 208 **Drug 1: PegIFN α-2b** *Dose*: 1.5 µg/kg/ week *Duration*: 18, 24, 30, 36, 42 or 48 wks* **Drug 2: Ribavirin** *Dose*: 800 – 1,400 mg/d *Duration*: 18, 24, 30, 36, 42 or 48 wks* *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)	**Total numbers involved**: 438 patients screened, 433 randomised **Treatment naïve / non-responders / relapsers:** Treatment naive **Previous treatment:** n/a **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 interferon alfa and/or ribavirin, anti-HCV positive, HCV RNA >1,000 IU/mL by quantitative reverse transcription PCR, increased serum ALT levels at screening, liver biopsy within preceding 24 months confirming chronic hepatitis, neutrophil ≥1,500 / µl and platelet counts ≥80,000 µl, 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, hep 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 x 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 (%)[a]:	**Primary outcomes**: SVR **Secondary outcomes**: • Sustained biochemical response (ALT normalisation at end of follow-up); • On-treatment virologic 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 week 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 <1,000 Iu/mL by the bDNA test. The cut off of 1,000 IU/mL instead of 615 IU/mL was chosen to improve the specificity of the bDNA assay. Patients with HCV RNA levels between 615 and 1,000 IU/mL but being HCV RNA negative on TMA were considered

		Group 1: 177 (87%) Group 2: 161 (85.1%) Fibrosis stage 3-4, n (%)[a]: Group 1: 34 (13%) Group 2: 31 (14.9%) Necroinflammatory score, mean (±SD): Not reported **Genotypes, n (%)**: 1: 100% **Gender male, n (%)**: Group 1: 128 (57) Group 2: 113 (54.3) **Age (yrs), mean ±SD, range** Group 1:42.8 ± 0.8, 18-73 Group 2: 42.7 ± 11.69 19 -66 **Ethnic groups, n (%)**: not reported **Mode of infection, n (%)**: not reported **Losses to follow up**: Group 1: Therapy and follow-up completed n=150 (67%) Therapy completed n=154 (68%) Follow-up completed n=189 (84%) Group 2: Therapy and follow-up completed n=135 (65%) Therapy completed n=145 (70%) Follow-up completed n=174 (84%) **Compliance**: Therapy discontinuations (n=71) Group 1: Therapy failure n=39 Adverse events n=7 Lost to follow-up n=24 Other reason n=1 Therapy discontinuations (n=63) Group 2: Therapy failure n=42 Adverse events n=4 Lost to follow-up n=15 Other reason n=2	bDNA undetectable after confirmation by re-testing. HCV genotyping performed by reverse hybridisation; histological results classified using standard criteria (Desmet 1994 cited).

Definitions:
RVR, rapid virological response (defined as HCV RNA negativity <615 IU/ml at week 4); EOT, end of treatment virological response; SVR, sustained virological response (defined as negative qualitative HCV RNA [<5.3 IU/ml by sensitive TMA assay] 24wks after the end of treatment); LVL low viral load (≤ 800,000 IU/ml); HVL, high viral load (>800,000 IU/ml).
Treatment failures: Breakthrough (reappearance of HCV viremia during antiviral treatment); Relapse (reappearance of HCV RNA during follow-up after stopping therapy in patients with an EOT virologic response); or Non-response (patients testing HCV RNA positive at any time point during the study). [a]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.

Outcome	Group 1 Standard (n=225) (48wks)	Group 2 Variable (n=208) (18 – 48 wks)	p-value
Viral Response, % (n/N), 95% CI			
4 wk (RVR)[b]	8.4[c] (19/225)	13.5[c] (28/208)	Not reported
RVR (wks 1-3 + wk 4)[d]	35[c] (78/225)	37[c] (76/208)	
12 wk (EVR)	-	-	
End of treatment	65 (146/225) 58.3 -71.1	64 (133/208) 57 - 70.5	Not reported
End of follow-up (SVR)	48 (108/225) 41.3 -54.7	35 (72/208), 28.2 - 41.5	0.005
SVR by RVR, % (n/N)[e]	42 (8/19)	57 (16/28)	Not reported
SVR by baseline viral load, % (n/N)	-	-	
SVR by baseline viral load[f] and RVR*, % (n/N)[g]			
<800,000 IU/mL (low)	75 (3/4)	69 (11/16)	Not reported
>800,000 IU/mL (high)	33 (5/15)	42 (5/12)	Not reported
Non-response % (n/N), 95% CI	18 (41/225) 13.4 - 23.9	20 (41/208) 14.5 - 25.8	Not reported
Virologic relapse % (n/N), 95% CI	14 (32/225) 9.9 - 19.5	33 (68/208) 26.4 - 39.5	<0.0005
Breakthrough % (n/N), 95% CI	5 (11/225) 2.5 - 8.6	3 (7/208) 1.4 - 6.8	Not reported
[b]time to first HCV RNA <615 IU/mL at week 4 by bDNA assay (not including those who became first negative between weeks 1-3); [c]Percentage calculated by reviewer from numbers presented in trial publication; [d]total number of patients first becoming HCV RNA negative between weeks 1 to 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 peginterferon alfa-2b.			
Biochemical response, % (n/N) End of treatment End of follow-up	Not reported		
Histology (proportion with improvement)	Not reported		
Adverse Events dose discontinuation for any adverse event dose reduction for any adverse event or lab abnormality	3% (7/225) 16%	2% (4/208) 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 interferon 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 ribavirin 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 rather than 24 weeks treatment. Treatment for less than 24 weeks in genotype 1 patients (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 viremia (≤ 800,000 versus >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 intention to treat: States an ITT analysis was conducted, though does not provide a definition of what they consider ITT 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 (though 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-square 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/drop-out: 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-naïve 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).
Inter-centre variability: Not reported
Conflict of interests: Not reported

Quality criteria for assessment (updated CRD guidance) **(answer yes/no/unclear)**

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, e.g. 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 drop-outs 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 intention to treat analysis? If so: - was this appropriate? - were appropriate methods used to account for missing data?	Yes Unclear Unclear

Mangia and colleagues[52]

Reference and Design	Intervention	Participants	Outcome measures
Ref ID: [52] **Author:** Mangia *et al.* **Year:** 2008 **Study design**: Multi-centre RCT **Number of centres:** 11 **Country**: Italy **Sponsor**: Not reported (but states no support was received from pharmaceutical companies)	**Intervention 1: Standard group (48wks)** n = 237 **Drug 1: PegIFN α-2a or α-2b** *Dose*: α-2a 180µg/ wk; α-2b 1.5 µg/kg/ wk. *Duration*: 48 weeks **Drug 2: Ribavirin** *Dose*: 1000mg/d for patients ≤75kg, 1200mg/d for patients >75kg *Duration*: 48 weeks **Intervention 2: Variable group (24, 48 or 72 wks*)** n = 459 **Drug 1: PegIFN α-2a or α-2b** *Dose*: α-2a 180µg/ wk; α-2b 1.5 µg/kg/ wk. *Duration*: 24, 48 or 72 weeks* **Drug 2: Ribavirin** *Dose*: 1000mg/d for patients ≤75kg, 1200mg/d for patients >75kg *Duration*: 24, 48 or 72 weeks* *treatment duration was based on time when HCV RNA first became undetectable; patients who were first HCV RNA-negative at: wk 4 treated for 24wks wk 8 treated for 48wks wk 12 treated for 72wks.	**Total numbers involved**: 711 enrolled, 696 randomised. n=237 Gp 1, n=459 Gp 2. **Treatment naïve / non-responders / relapsers:** treatment naïve **Previous treatment:** n/a **HCV/HIV co-infection:** no **Recruitment**: 11 centres in southern Italy between June 2004 and December 2005 **Inclusion criteria**: previously untreated adults (18-70 yrs) with compensated chronic HCV genotype 1, anti-HCV-positive, HCV RNA-positive, neutrophil count ≥1500µL, platelet count ≥90,000µL, haemoglobin ≥12g/dl for women and ≥13g/dl for men, creatinine <1.5mg/dL. **Exclusion criteria:** other causes of liver disease, Hep 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 (%):** <400,000IU/mL: 62 (26%) Gp 1, 103 (22%) Gp 2, p=0.30 ≥400,000IU/mL: 175 (74%) Gp 1, 356 (78%) Gp 2 **Serum ALT, n (%):** <3 unl*: 193 (81%) Gp 1, 385 (84%) Gp 2, p=0.39 ≥3 unl: 44 (19%) Gp 1, 74 (16%) Gp 2 **Histology**: Fibrosis stage, n (%):[a] 0-2: 140 (62%) Gp 1, 258 (65%) Gp 2, p=0.33 3-4: 87 (38%) Gp 1, 134 (34%) Gp 2 [a]data unavailable from 67 patients (10 Gp 1, 57 Gp 2) Grade of activity, n (%):[b] 0-2: 167 (76%) Gp 1, 306 (78%) Gp 2, p=0.42 3: 54 (24%) Gp 1, 89 (22%) Gp 2 [b]data unavailable from 78 patients (14 Gp 1, 64 Gp 2)	**Primary outcomes**: SVR **Secondary outcomes**: • SVR according to virological response at at wks 4, 8 & 12 • RVR • EOT (end of treatment virological response) • adverse events **Length of follow up**: 24 wks 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 low 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.

		Steatosis:[c] Yes: 70 (31%) Gp 1, 103 (26%) Gp 2, p=0.07 No: 151 (68%) Gp 1, 295 (74%) Gp 2 [c]data missing from 67 patients (6 Gp 1, 61 Gp 2) **Genotypes, n (%)**: 1a: 15 (6%) Gp 1, 49 (11%) Gp 2, p=0.08 1b: 222 (94%) Gp 1, 410 (89%) Gp 2 **Gender, n (%)**: Female: 105 (44%) Gp 1, 201 (44%) Gp 2, p=0.93 Male: 132 (56%) Gp 1, 258 (56%) Gp 2 **Age (yrs), mean (±SD)**: 52.6 (±11.8) Gp 1, 51.1 (±12.1) Gp 2, p=0.12 **Ethnic groups, n (%)**: not reported **Mode of infection, n (%)**: Blood transfusion: 50 (21%) Gp 1, 93 (20%) Gp 2 Drug abuse: 17 (7%) Gp 1, 37 (8%) Gp 2, p=0.81 Unknown: 170 (72%) Gp 1, 329 (72%) Gp 2 **Treatment, n (%):** Peg 2b: 127 (53%) Gp 1, 235 (51%) Gp 2, p=0.52 Peg 2a: 110 (46%) Gp 1, 224 (49%) Gp 2 **Losses to follow up**: n=6 (Gp 2) **Compliance**: n=83 (12%) discontinued treatment (24 Gp 1, 59 Gp 2) due to adverse events (16 Gp 1, 30 Gp 2) or no compliance (8 Gp 1, 29 Gp 2).	

Definitions: SVR, sustained virological response (defined as undetectable serum HCV RNA at the end of 24wks follow-up); RVR, rapid virological response (defined as HCV RNA negative at wk 4); EOT, end of treatment virological response; non-responders defined as patients who were viraemic at wk 24 and also patients with a <2 log decline at wk 12; treatment failures defined as relapse (reappearance of HCV RNA during follow-up period after an EOT response), non-response or discontinuation; *unl, upper normal limit.

Outcome	**Gp 1 Standard (n=237) (48wks)**	**Gp 2 Variable (n=123) (24wks)**	**p-value**
NOTE: data has only been extracted for Gp 1 vs 24wk subset of Gp 2, as results for Gp 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%–100%)	95.1% (117/123, 92.3%-99.4%)	0.42
SVR by RVR	87.1% (54/62, 78.7%-95.4%)	77.2% (95/123, 69.8%-84.6%)	0.12; difference -9.9% (10.5% - 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) Relapse rate by RVR, % (n/N)	19.1% (25/131) 10% (6/62)	19.4% (54/278) 18.8% (22/123) (*Reviewer: should be 17.9%*)	1.0 0.13
Biochemical response, % (n/N)	not reported	not reported	
Histology (proportion with improvement)	not reported	not reported	
Adverse Events **(for Gp 1 vs Gp 2, not 24wk subset of Gp 2)** dose discontinuation: for any adverse event for no compliance dose reduction Specific adverse events, n (%): asthenia flu-like symptoms dermatological symptoms psychiatric symptoms anaemia leukopenia & thrombocytopenia thyroid diseases decrease in Hb to <9.5g/dL neutrophil count <1000/mm^3 (requiring Peg-IFN dose reduction)	**Gp 1, 48 wks, n=237** 24 (10.1%) 16 (6.7%) 8 (3.4%) 32 (13.5%) 101 (42.6%) 34 (14.3%) 29 (12.2%) 4 (1.7%) 20 (8.4%) 58 (24.4%) 7 (2.9%) 20 (8.4%) 12 (5.1%)	**Gp 2, 24, 48 or 72 wks n=459** 59 (12.9%) 30 (6.5%) 29 (6.3%) 47 (10.2%) 183 (39.8%) 87 (18.9%) 60 (13.0%) 7 (1.5%) 33 (7.1%) 35 (7.6%) 11 (2.3%) 33 (7.1%) 19 (4.1%)	 0.19 0.49 0.66 0.69

Additional Results/comments (e.g., early response factors, quality of life):
Virological response

- Results for EOT, SVR and predictive factors were reported for Gp 1 vs Gp 2, as well as Gp 1 vs the 48wk and 72wk subsets of Gp 2, but these have not been extracted.
- In the entire population (n=696), 185 (26.6%) had undetectable HCV RNA at wk 4 (i,e, RVR), comprising 62 (26.2%) Gp 1 and 123 (26.8%) Gp 2 (whole Gp), 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 2b and 24% (80/334) patients treated with Peg 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 <400,000iu/mL (odds ratio 2.27, 95% CI 1.49-3.41) and absence of advanced fibrosis (odds ratio 1.40, 95% CI 1.15-1.64).
- The only independent predictor of SVR in RVR patients was a mild to moderate degree of fibrosis (odds ratio 2.60, 95% CI 1.09-6.17). 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 5 using a computer-generated randomisation list that was sent to each participating centre. Peg-IFN 2a or 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 intention to treat: ITT analysis - all randomised patients who received at least 1 dose of study medication were used for analysis of primary and secondary outcomes.
Comparability of treatment groups at baseline: participant baseline demographic, biological and virologic characteristics were well matched between Gp 1 vs Gp 2 with no statistically significant differences (p-values reported). Also reports that baseline characteristics did not differ between patients treated with Peg 2a and Peg 2b (but data not presented). However, comparability of Gp 1 (48wks) vs 24wks 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 χ^2 test and the *t* test (continuous data). Level of significance was 0.05 (2-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 1-sided 95% CI and 80% power. With a drop-out rate of 10%, 237 patients per group were required. Given that the secondary aim of investigating SVR rates according to on-treatment virologic response, double this number (474) of patients were assumed to be recruited into the variable group for meaningful sub-group comparisons. **Important note:** only 69 (9.9%) patients (24 Gp 1, 45 Gp 2 24wks subset) had LVL (<400,000IU/mL) and RVR and thus the study was likely not powered for this sub-group.
Attrition/drop-out: 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 Fig.1 & Table 3. Fig. 1 reports 144 completed, 24 discontinued, 69 HCV RNA +ve at wk 24 (Gp 1); 297 completed, 59 discontinued, 103 HCV RNA +ve at wk 24 (Gp 2). Table 3 reports 122 completed treatment, 24 discontinued, 91 no response at wk 24 (Gp 1); 237 completed treatment, 59 discontinued, 163 no response at wk 24 (Gp 2).

General comments
Generalisability: treatment-naïve, Italian patients with genotype 1 HCV. Only 24% had LVL at baseline and only 10% had LVL and RVR.
Inter-centre variability: reports that HCV RNA testing carried out at individual centres provided that all centres used the same assay. However, no inter-centre 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 a not a standard 48wk vs 24wk study in genotype 1 patients as Gp 2 included patients treated for 24, 48 and 72 wks, 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 sub-group, but results should be treated with caution.

Quality criteria for assessment (updated CRD guidance) **(answer yes/no/unclear)**

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, e.g. severity of disease?	Yes (Gp 1 vs Gp 2); Unclear for Gp 1 vs 24wk 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 drop-outs 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 intention to treat analysis? If so: - was this appropriate? - were appropriate methods used to account for missing data?	Yes Yes Unclear

Liu and colleagues[53]

Reference and Design	Intervention	Participants	Outcome measures
Ref ID: [53], [57] **Author:** Liu *et al*. Liu *et al*. (abstract) **Year:** 2008 2008 abstract **Study design**: Open-label, multi-centre RCT **Number 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: Peginterferon-α- 2a** *Dose*: 180µg/ week s.c. *Duration*: 24 weeks **Drug 2: Ribavirin** *Dose*: 1000mg/day for body weight < 75kg and 1200 mg/day for body weight ≥ 75kg *Duration*: 24 weeks **Group 2: 48 weeks** n = 154 **Drug 1: Peginterferon-α- 2a** *Dose*: 180µg/ week s.c. **Duration*: 48 weeks **Drug 2: Ribavirin** *Dose*: 1000mg/day for body weight < 75kg and 1200 mg/day for body weight ≥ 75kg *Duration*: 48 weeks * Treatment was prematurely discontinued in patients who were randomised to 48 weeks of treatment but who continued to have HCV viremia at week 24 of therapy, because they had minimal chance of achieving SVR with continued therapy.	**Total numbers involved**: 308 patients n=154 Gp 1, n=154 Gp 2 **Treatment naïve / non-responders / relapsers:** Treatment naive **Previous treatment:** n/a **HCV/HIV co-infection:** no **Recruitment**: 5 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 histologic characteristics consistent with chronic viral hepatitis within the last three months **Exclusion criteria:** Anaemia: <13g/dL for men; <12 g/dL for women, neutropaenia (neutrophil count <1500 cells/mm^3), thrombocytopaenia (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), decompensated cirrhosis (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 (Gp 1), 5.8 ± 0.7 (Gp 2), p=0.83 **Serum ALT: mean value x ULN ± sd** 3.2 ± 2.6 (Gp 1),3.0 ± 2.1 (Gp 2), p=0.91 **Histology**: Fibrosis score n (%): ≥3: 121 (78.6) (Gp 1), 117 (76.0) (Gp 2) p=0.68 6: 35 (22.7) (Gp 1), 31 (20.1) (Gp 2) p=0.68 [≥ 3 is significant fibrosis, 6 is cirrhosis]	**Primary outcomes**: SVR rate **Secondary outcomes**: • RVR • EVR • EOT virologic response • Relapse rate • ALT normalisation • Histologic 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, wks 4, 12, end of treatment and 24 wks after end of treatment (lower limit of detection 25 IU/ml). Patients in 48 wks group had an additional HCV RNA test at wk 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 histological activity index (HAI).

		Mean total modified HAI score, (±SD): 12.7 ± 3.3 (Gp 1), 12.3 ± 3.7 (Gp 2), p=0.43 **Genotypes, n (%)**: 1a: 4 (2.6%) Gp 1, 3 (1.9%) Gp 2 1b: 143 (92.9%) Gp 1, 145 (94.2%) Gp 2 1a & 1b: 7 (4.5%) Gp 1, 6 (3.9%) Gp 2 **Gender male, n (%)**: 88 (57.1) (Gp 1), 87 (56.5) (Gp 2), p>0.99 **Age (yrs), mean (range)**: 54 ± 10 (Gp 1), 53 ± 11 (Gp 2), p=0.41 **Ethnic groups, n (%)**: Asian (no further details reported) **Mode of infection, n (%)**: Not reported **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**: Not reported.	

Definitions: s.c., subcutaneous; ULN, upper limit of normal; ALT, alanine aminotransferase; RVR, rapid virological response defined as an undetectable serum HCV RNA level (<25 IU/mL) at week 4 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. Complete EVR was defined as 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; End of treatment virologic response defined as an undetectable serum HCV RNA at the end of treatment; SVR, sustained virological response defined as an undetectable serum HCV RNA at the end of the follow-up period; histologic response rate defined as at least 2 point reduction in the modified histologic 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.

Outcome	**Group 1 (24 wks treatment)**	**Group 2 (48 wks treatment)**	**p-value**
Viral Response, n (%)			
4 wk (RVR)	104 (68)	97 (63)	0.47
12 wk (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 24wk Gp, and 62%, 96%, 92%, 75% and 15% for 48 wk Gp.			
Predictability of SVR during treatment with RVR stratified by baseline viral load	SVR	SVR	
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
Histologic response, n (%)	71 (59)			97 (78)			0.001
	RVR			SVR			
	Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis		
	P	OR (95% CI)	P	P	OR (95% CI)	P	
HCV RNA level (<800, 000 vs. ≥ 800, 000 IU/mL)	<0.001	3.33 (1.96-5.64)	<0.001	<0.001	10.51 (5.47-20.21)	<0.001	
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*	19 (19)			46 (30)			
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)			
*weight reduction of >10% from the baseline weight (p=0.03)							

Adverse events:

- In the 24 wks group, severe adverse events included retinal ischemia, hepatic decompensation, major depression and hepatocellular carcinoma (the first three events were considered to be treatment related). In the 48 wk group, severe adverse events included hepatic decompensation in 3 patients and major depression, renal abscess, interstitial pneumonitis, diabetes mellitus, empymea, pulmonary tuberculosis, hepatocellular carcinoma, and acute pancreatitis in 1 patient each (the first nine events were considered to be treatment related)

- Fifteen patients experienced serious AEs 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 peginterferon. 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 weeks 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: Not reported.
Blinding: Open label trial. Biopsy pathologist was blind to clinical status of study participants. Not stated whether other outcome assessors were blinded.
Analysis by intention to treat: Authors state analysis was by intention to treat, for the primary efficacy endpoint. The secondary efficacy end points were analyzed 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 viremia at week 24 of therapy, because they had minimal chance of achieving SVR with continued therapy. 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 x^2 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 <0.5 was considered to be statistically significant, all statistical tests were 2 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 α =.05 and a type II error rate of β = .20 for a primary 2 sided test with the assumption of a 15% difference in SVR rates (60% and 75% for 24 and 48 weeks of treatment respectively).
Attrition/drop-out: Participants were considered withdrawn from the study if the investigator was concerned about treatment safety or if the patient missed 4 consecutive weeks of therapy. In Gp 1, seven patients discontinued treatment, six due to adverse events or laboratory abnormalities, one declined treatment. In Gp 2 four discontinued treatment due to adverse events or laboratory abnormalities. Fifteen patients in Gp 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 (Gp 1) and $\log_{10}$ 5.8 = 630,957 IU/ml (Gp 2)] was low and approx. 65% at RVR at week 4.
Inter-centre variability: Not reported.
Conflict of interests: One author has been a consultant for Novartis and Roche, one author has been a consultant for Novartis and Glaxo SmithKline (GSK). Another has been a consultant for Bristol-Myers Squibb, 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) **(answer yes/no/unclear)**

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, e.g. 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 drop-outs 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 intention to treat analysis? If so:	Yes

- was this appropriate? - were appropriate methods used to account for missing data?	-Yes -Unclear

Yu and colleagues (2008)[54]

Reference and Design	Intervention	Participants	Outcome measures
Ref ID: [54] [58](abstract) **Author:** Yu *et al.* **Year:** 2008 (2007) abstract **Study design**: Open label, multi-centre RCT **Number of centres:** Four **Country**: Taiwan **Sponsor**: Taiwan Liver Research Foundation	**Group 1: 24 weeks** n = 100 **Drug 1:** **Peginterferon α-2a** *Dose*: 180 µg/week s.c. *Duration*: 24 weeks **Drug 2: Ribavirin** *Dose*: 1000mg/day for body weight ≤75kg and 1200 mg/day for body weight >75kg, oral, 2 divided doses *Duration*: 24 weeks **Group 2: 48 weeks** n = 100 **Drug 1:** **Peginterferon α-2a** *Dose*: 180 µg/week s.c. *Duration*: 48 weeks **Drug 2: Ribavirin** *Dose*: 1000mg/day for body weight ≤75kg and 1200 mg/day for body weight >75kg, oral, 2 divided doses *Duration*: 48 weeks	**Total numbers involved**: 200 Intervention 1: 100 Intervention 2: 100 **Treatment naïve / non-responders / relapsers:** Treatment naive **Previous treatment:** n/a **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 yr before entry, elevated serum ALT for ≥ 2 measurements within 6 months before trial entry, genotype 1 infection, neutrophil count >1500 mm^{-3}, platelet count > $9x10^4$ mm^{-3}, haemoglobin level > 12 g/dL men and >11 /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, scelorisng cholangitis, Wilson disease, $alfa_1$-antitryspin deficiency, decompensated cirrhosis, overt hepatic failure, a current or history of alcohol abuse (≥ 20g daily), psychiatric conditions, previous liver transplantation, or with evidence of hepatocellular carcinoma **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 **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	**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 exam 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

		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 (yrs), mean (± SD)**: Group 1: 49.7 ± 11.6 Group 2: 49.1 ± 12 p value = 0.729 **Ethnic groups, n (%)**: not reported **Mode of infection, n (%)**: not reported **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**: not reported	

Definitions: Rapid virological reponse (RVR) was defined by PCR-negative serum HCV RNA (<50 IU/mL) at 4 weeks of therapy. Early virological response (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. End of treatment (EOT) virological response was defined as PCR-negative serum HCV-RNA (<50 IU/mL) at the end of treatment. Sustained virological response (SVR): defined as HCV RNA PCR-seronegative by the end of treatment and throughout the follow up period Relapse was defined as HCV RNA reappearance during the follow up period in patients who achieved an end of treatment virological response. Serum HCV RNA at baseline, wks 4, 12 end of treatment and 24 wks after therapy were determined by qualitative PCR, levels at baseline and week 12 of treatment were measure using the branched DNA assay (Versant HCV RNA 3.0, Bayer, Tarrytown, NJ; quantification limit: 615 IU/mL).

Outcome	**Group 1, 24 week treatment (n=100)**	**Group 2, 48 week treatment (n=100)**	**p-value**
Viral Response, % (95% CI, %)			
4 wk (RVR) EVR End of treatment Relapse End of follow-up (SVR)	45 (35 - 55) 95.9 (92 - 100) 93 (88 - 98) 36.6 (27 -47) 59 (49 - 69)	42 (32-52) 93 (88 - 98) 90 (84 - 96) 12.2 (5- 19) 79 (71-87)	 <0.0001 0.002
SVR by RVR: RVR, % (n/N, 95% CI) No RVR, % (n/N, 95% CI)	 88.9 (40/45, 0.8- 0.98) 34.5 (19/55, 0.22 – 0.47)	 100 (42/42) 63.8 (37/58 0.51- 0.76)	 0.056[1] 0.002[2]
	[1] difference 11.1%, (95% CI -22.6% to 4.2%) [2] difference 29.2 % (95% CI -48% to -13.4%)		
	Group 1: 24 weeks	**Group 2: 48 weeks**	

SVR by viral load and RVR, % (n/N, 95% CI) RVR and LVL (n =52) RVR and HVL (n = 35)	 96.4% (27/28, 89-103%) 76.5% (13/17, 56-97%)	 100% (24/24) 100% (18/18)	 difference -3.6% (-14.3% to -0.6%) p=1.000 p=0.045
Relapse rate, % (n/N, 95% CI) Relapse rate by RVR RVR no RVR Relapse rate by viral load and RVR, % (n/N, 95% CI) RVR and LVL (n=52) RVR and HVL (n=35)	36.6% (34/93, 27- 47%) 11.1% (5/45, 0.02-0.2%) 60.4% (29/48, 0.46-0.74%) 3.6% (1/28, -3 – 11%) 23.5% (4/17, 3-44%)	12.2% (11/90, 5-19%) 0 (0/42) 22.9% (11/48, 0.11-0.35%) 0 (0/24) 0 (0/18)	p<0.0001 difference 11.1% (-0.4% to 18%) difference 37.5% (17.2% to 53.7%) difference 3.6 % (-7.2% to 6.6%) p=1.000 p=0.045
Adverse Events n (%) Serious adverse events Discontinuation Dose modification or transient interruption for adverse events or laboratory abnormalities: Peginterferon- α-2a Ribavirin Peginterferon- α-2a or ribavirin Influenza like symptoms including fever, chills, headache Gastrointestinal symptoms Anorexia or nausea Diarrhoea Psychiatric symptoms Anxiety Depression Insomnia Dermatological symptoms Hair loss Skin rash Hematological abnormality Leukopenia (white cell count <1500mm^{-3}) Anemia (haemoglobin <10 g/dl) Thrombocytopenia (<50 mm^{-3}) Abnormal thyroid function tests	 1% (1) 3 (3) 22 (22) 49 (49) 54 (54) 76 (76) 50 (50) 18 (18) 31 (32) 24 (24) 59 (59) 66 (66) 54 (55) 5 (5) 39 (39) 2 (2) 13 (13)	 1% (1) 10* (10) 24 (24) 60 (60) 65 (65) 74 (74) 53 (53) 26 (26) 36 (36) 34 (34) 65 (65) 72 (72) 66 (66) 8 (8) 48 (48) 6(6) 15 (15)	 0.045 0.737 0.118 0.113 0.744 0.671 0.172 0.454 0.119 0.382 0.359 0.083 0.39 0.199 0.279 0.684
	Serious AE: 1 patient with cirrhosis experienced variceal bleeding at EOT, 1 patient experienced severe myalgias over the lower back, resulting in disability of gait during treatment. *8 of these were due to adverse events, 1 to insufficient serum creatinine level and 1 because of insufficient response		

Additional Results/comments:

	SVR (-)	SVR (+)	SVR (-)	SVR (+)

Baseline HCV RNA level, log IU/mL	5.92 ± 0.60	5.09 ± 1.08[a]	5.93 ± 0.86	5.58 ± 0.96[b]
<400,000 IU/mL, n (%)	11 (26)	34 (57.6)[c]	8 (38.1)	36 (45.6)[d]
≥400,000 IU/mL, n (%)	30 (73.2)	25 (42.4)[e]	13 (61.9)	43(54.4)[e]

[a] p<0.0001 between those with and without SVR in 24 week group (Group 1)
[b] p= 0.132 between those with and without SVR in 48 week group (Group 2)
[c] p=0.002 between those with and without SVR in 24 week group (Group 1)
[d] p=0.540 between those with and without SVR in 48 week group (Group 2)
[e] p value not reported

Additional results/ comments, continued:

- 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 – 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 were significant and are not presented here.
- In the 24 week group, RVR (p<0.0001), lower viremia (<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: latter 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 viremia with odds ratios (CI) of 10.84 (3.189-36.82) and 3.087 (1.031 – 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 viremia or without an RVR the relapse rate was significantly higher in the 24 week group (50.8%, 95% CI 39-63%) than in the 48 week group (16.7%, 95% CI 8-26%) p<0.0001). The SVR rate was significantly lower in the 24 week group (44.4%, 95% CI 33 – 56%) than in the 48 week group (71.4% 95% CI 62-82%, p=0.001).

Methodological comments:
Allocation to treatment groups: Randomly by computer coding, 1:1 randomization 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 intention to treat :*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% drop out rate.
Attrition/drop-out: 199/ 200 patients completed the study. One patient in the 48 week group was lost to follow-up two months after cessation of treatment and was classified as a non-responder for final analysis.

General comments
Generalisability: The study appears generalisable to treatment naïve, Asian patients with genotype 1 HCV. Mean base line viral load (log 5.43 = 269,153 IU/ml and log 5.66=457, 088IU/ml for 24 weeks and 48 weeks respectively) was low and approx. 55% had LVL (<400,000 IU/mL). Approx 43% had RVR at wk 4.
Inter-centre variability: Not reported.
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) **(answer yes/no/unclear)**

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, e.g. 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 drop-outs 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 intention to treat analysis? If so: - was this appropriate? - were appropriate methods used to account for missing data?	Yes Yes Yes

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Reference and Design	Intervention	Participants	Outcome measures
Ref ID: [55] **Author:** Yu *et al*. **Year:** 2007 **Study design**: Open-label, multi-centre RCT **Number of centres:** 4 **Country**: Taiwan **Sponsor**: Taiwan Liver Research Foundation	**Intervention 1: 24wks** n = 100 **Drug 1: PegIFN α-2a** *Dose*: 180µg once/week, subcutaneous *Duration*: 24 weeks **Drug 2: Ribavirin** *Dose*: 1000mg/d for patients ≤75kg, 1200mg/d for patients >75kg (oral, two divided doses) *Duration*: 24 weeks **Intervention 2: 16wks** n = 50 **Drug 1: PegIFN α-2a** *Dose*: 180µg once/week, subcutaneous *Duration*: 16 weeks **Drug 2: Ribavirin** *Dose*: 1000mg/d for patients ≤75kg, 1200mg/d for patients >75kg (oral, two divided doses) *Duration*: 16 weeks	**Total numbers involved**: 326 screened, 150 eligible and randomised. n=100 Gp 1, n=50 Gp 2. **Treatment naïve / non-responders / relapsers:** treatment naïve **Previous treatment:** n/a **HCV/HIV co-infection:** no **Recruitment**: a medical centre and 3 regional core hospitals in Taiwan between September 2003 and December 2005 **Inclusion criteria**: previously untreated adults (18-65 yrs) with HCV genotype 2, seropositive for HCV antibodies and for HCV RNA PCR, undergone liver biopsy within 1 yr before entry (with result of chronic hep C), increased serum ALT defined as ≥1.5 times the ULN for ≥2 measurements within 6 mths preceding trial entry, neutrophil count >1500/mm^3, platelet count >9 x 10^4/mm^3, haemoglobin >12g/dl for men and 11g/dl for women, serum creatinine <1.5mg/dl, no pregnancy or lactation and using reliable contraception for women. **Exclusion criteria:** HCV genotype other than type 2, hep B surface antigen HIV infection, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, Wilson's disease α-antitrypsin deficiency, decompensated cirrhosis (Child-Pugh class B or C), overt hepatic failure, current or history of alcohol misuse (≥20g/d) psychiatric condition, previous liver transplant, evidence of HCC. **Baseline measurements**: **Viral load (log IU/ml), mean (±SD):** 4.88 (1.07) Gp 1, 4.98 (1.08) Gp 2, p=0.62 **Serum ALT (IU/l), mean (±SD):** 108.9 (68.75) Gp 1, 107 (64.6) Gp 2, p=0.857 **Histology**: Fibrosis, n (%): p=0.832 F 0-2: 80 (80) Gp 1, 39 (78) Gp 2 F 3-4: 20 (20) Gp 1, 11 (22) Gp 2 Necroinflammatory score, mean (±SD): 4.84 (2.34) Gp 1, 5.48 (3.32) Gp 2, p=0.226 Steatosis, n (%): p=1 None (0): 67 (67) Gp 1, 34 (68) Gp 2 Mild (1): 28 (28) Gp 1, 13 (26) Gp 2	**Primary outcomes**: SVR **Secondary outcomes**: • RVR • ETVR (end of treatment virological response) • relapse rate • adverse events **Length of follow up**: 24 wks after cessation of treatment **Methods of assessing outcomes:** patients had bi-monthly out-patient visits during the 1st month and monthly visits thereafter where they underwent a physical exam 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 wk 4 were measured using the branched DNA assay, quantification limit 615 IU/ml. Serum HCV RNA at baseline, during treatment wks 4, 12, end of treatment and at follow-up was determined by standardised automated qualiltative PCR, detection limit 50 IU/ml. Scheuer and Knodell scoring system used for liver histology.

		Mod - severe (2-3): 5 (5) Gp 1, 3 (6) Gp 2 **Genotypes, n (%)**: 100% genotype 2 **Gender male, n (%)**: 58 (58%) Gp 1, 32 (64%) Gp 2 **Age (yrs), mean (±SD):** 49.9 (10.69) Gp 1, 50.8 (9.74) Gp 2, p=0.621 **Ethnic groups, n (%)**: 100% Asian (Taiwanese) **Mode of infection, n (%)**: not reported **Losses to follow up**: 0 **Compliance**: **80/80/80 adherence, n (%)**: 73 (73) Gp 1, 43 (86) Gp 2	

Definitions: Gp, group; ULN, upper limit of normal; ALT, alanine transaminase level; 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; SVR, sustained virological response (defined as PCR-negative serum HCV RNA by end of treatment and end of follow-up); RVR, rapid virological response (defined as PCR-negative serum HCV RNA at 4 weeks of treatment); ETVR, end of treatment virological response (defined as PCR-negative serum HCV RNA at end of treatment); 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.

Outcome	**Intervention 1 (24wks)**	**Intervention 2 (16 wks)**	**p-value**
Viral Response, % (n/N, 95% CI)			
4 wk (RVR)	87% (87/100, 80%-94%)	86% (43/50, 76%-96%)	
12 wk (EVR)	-	-	
End of treatment (ETVR)	98% (98/100, 95%-100%)	100%	
End of follow-up (SVR)	95% (95/100, 91%-99%)	94% (47/50, 87%-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)	not reported	not reported	
Other viral response outcomes:			
Relapse rate, % (n/N, 95% CI)	3.1% (3/98, -1%-13%)	6% (3/50, 0-7%)	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):			0.554
RVR	2.3% (2/87)	0 (0/43)	0.245
No RVR	9.1% (1/11)	42.9% (3/7)	

Biochemical response, % (n/N) End of treatment End of follow-up	not reported	not reported	
Histology (proportion with improvement) Inflammation mean change Fibrosis mean change	not reported	not reported	
Adverse Events, n (%) Dose discontinuation for any adverse event Dose modification for adverse events or lab abnormalities: Peg RBV Peg or RBV Specific adverse events Flu-like symptoms: fever chills headache Gastrointestinal symptoms: anorexia nausea diarrhoea Psychiatric symptoms: anxiety depression insomnia Dermatological symptoms: hair loss skin rash Haematological abnormality: leucopenia (white cell count <1500/mm^3) anaemia (Hb <10g/dl) thrombocytopaenia (<50,000/mm^3) Abnormal thyroid function tests	 1 (1%) 9 (9%) 51 (51%) 54 (54%) 55 (55%) 28 (28%) 39 (39%) 46 (46%) 15 (15%) 9 (9%) 7 (7%) 10 (10%) 57 (57%) 49 (49%) 54 (54%) 2 (2%) 53 (53%) 1 (1%) 13 (13%)	 0 4 (8%) 23 (46%) 26 (52%) 29 (58%) 12 (24%) 21 (42%) 20 (40%) 3 (6%) 5 (10%) 4 (8%) 3 (6%) 23 (46%) 10 (20%) 22 (44%) 1 (2%) 27 (54%) 0 4 (8%)	 1 1 0.564 0.817 0.727 0.602 0.724 0.601 0.181 1 1 0.545 0.227 0.001 0.248 1 0.908 1 0.362
Additional Results/comments (e.g., early response factors, quality of life): *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 wks Gp (4.86 ± 1.08 vs 5.33 ± 0.55, p=0.342) and the 16 wks Gp (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 wks compared to those who did not achieve an SVR in both the 24wks Gp (90% (85/95) vs 40% (2/5), p=0.015) and the 16 wks Gp (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 16wks Gp (42.9%, 95% CI -7% to 92%) than in the 24wks Gp (9.1%, 95% CI -11% to 29%), and the SVR rate was lower in the 16 wks Gp (57%, 95% CI 20% to 94%) than in the 24wks Gp (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 peginterferon and RBV) on the SVR rate were			

reported in the publication, but none were significant and 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 were significant.
- Results were reported for mean ribavirin 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 (24wks Gp) due to anaemia and leucopenia at wk 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: Pts 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 intention to treat: 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 16wks Gp had slightly higher 80/80/80 adherence compared to 24wks Gp (86% vs 73%, p=0.073), but the difference wasn't significant.
Method of data analysis: Frequency was compared between groups using the χ^2 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 v 12.0). All statistical analyses were based on 2-sided hypothesis tests with a significance level of $p<0.05$.
Sample size/power analysis: Assuming an SVR rate of 82% for 24wks 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/drop-out: Reasons for the 1 dropout were provided.

General comments
Generalisability: treatment-naïve, 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 24wks and 16wks respectively) was low, and when SVR was measured (at 24wks follow-up) approx 83% had baseline LVL (<800,000 IU/ml). The majority (86%) had RVR at wk 4.
Inter-centre variability: not reported.
Conflict of interests: none.

Quality criteria for assessment (updated CRD guidance) **(answer yes/no/unclear)**

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, e.g. 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 drop-outs 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 intention to treat analysis? If so: - was this appropriate? - were appropriate methods used to account for missing data?	Yes Yes Yes

von Wagner and colleagues[56]

Reference and Design	Intervention	Participants	Outcome measures
Ref ID: [56] **Author:** von Wagner *et al.* **Year:** 2005 **Study design**: Multi-centre, phase IIIb RCT **Number of centres:** 6 **Country**: Germany **Sponsor**: Hoffmann-La Roche and the German Hepatitis Network of Competence (Hep-Net)	n=153 **Peg IFN α-2a** *Dose*: 180 µg/week, subcutaneous *Duration*: 8 weeks **RBV** *Dose*: 800 mg/d for patients ≤65kg, 1000 mg/d for patients 65-85kg, 1200 mg/d for patients >85kg, oral *Duration*: 8 weeks Those with rapid virological response (RVR) at wk 4 randomised at wk 8 to: **Intervention 1: 16wks, RVR (Group A)** n = 71 **Drug 1: PegIFN α-2a** *Dose*: 180µg/week, subcutaneous *Duration*: 8 weeks **Drug 2: Ribavirin** *Dose*: 800mg/d for patients ≤65kg, 1000mg/d for patients 65-85kg, 1200mg/d for patients >85kg; oral *Duration*: 8 weeks (total duration 16 wks) **Intervention 2: 24wks, RVR (Group B)** n = 71 **Drug 1: PegIFN α-2a** *Dose*: 180µg/week, subcutaneous *Duration*: 16 weeks **Drug 2: Ribavirin** *Dose*: 800mg/d for patients ≤65kg, 1000mg/d for patients 65-85kg, 1200mg/d for patients >85kg; oral *Duration*: 16 weeks (total duration 24 wks) Patients without an RVR at wk 4 allocated at wk 8 to: **Intervention 3: 24wks, no RVR (Group C)*** n = 11 **Drug 1: PegIFN α-2a**	**Total numbers involved**: 153 enrolled; 142 randomised at wk 8 (Gp A & B). **Treatment naïve / non-responders / relapsers:** treatment naïve **Previous treatment:** n/a **HCV/HIV co-infection:** no **Recruitment**: 6 tertiary referral centres in Germany between Jan 2002 and Mar 2004 **Inclusion criteria**: adults (>18yrs), not previously treated with interferon and/or ribavirin, with compensated chronic HCV genotype 2 or 3, positive for anti-HCV antibody and HCV RNA >600 IU/ml, liver biopsy within 18mths prior to screening, ≥1 serum ALT level elevated at screening or study entry, neutrophil count ≥1500/µL, platelet count ≥90,000/µL, haemoglobin ≥13g/dl for men and ≥12g/dl for women. **Exclusion criteria:** any other cause of liver disease or other relevant disorders including HIV or Hep B co-infection, clinically significant haematologic, hepatic, metabolic, renal, rheumatologic, neurologic 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) Gp A 5.8 (±0.8) Gp B 5.7 (±0.5) Gp C **Serum ALT x ULN (IU/l), mean (±SD):** 2.8 (±2.9) Gp A 2.8 (±2.0) Gp B 2.4 (±0.9) Gp C **Histology**: Classification system used: Ishak Fibrosis score, mean (±SD):	**Primary outcomes**: SVR **Secondary outcomes**: • RVR • end of treatment virological response • sustained biochemical response • virological response according to genotype and baseline viraemia • adverse events **Length of follow up**: 24 wks after end of treatment **Methods of assessing outcomes:** evaluated at wks 2, 4, 8, 12, 16, 20 and 24 (Gp B & C) during treatment and at wks 4, 12 & 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 50IU/ml). HCV genotyping performed by reverse hybridisation; histology classified according to Ishak.

	Dose: 180µg/week, subcutaneous *Duration*: 16 weeks **Drug 2: Ribavirin** *Dose*: 800mg/d for patients ≤65kg, 1000mg/d for patients 65-85kg, 1200mg/d for patients >85kg; oral *Duration*: 16 weeks (total duration 24 wks) (*not randomised)	1.6 (±1.4) Gp A 1.6 (±1.1) Gp B 2.4 (±2.3) Gp C Necroinflammatory score (total inflammation), mean (±SD): 4.3 (±2.4) Gp A 4.6 (±2.4) Gp B 5.0 (±4.0) Gp C **Genotypes, n (%)**: Genotype 2 Genotype 3 19/71 (27%) Gp A* 51/71 (72%) Gp A 19/71 (27%) Gp B 52/71 (73%) Gp B 1/11 (9%) Gp C 10/11 (91%) Gp C (*G2 or 3 could not be differentiated in 1 patient) **Gender male, n (%)**: 52 (73%) Gp A 41 (58%) Gp B 4 (36%) Gp C **Age (yrs), mean (±SD)**: 38 (±9) Gp A 39 (±11) Gp B 42 (±10) Gp C **Ethnic groups, n (%)**: not reported **Mode of infection, n (%)**: not reported **Losses to follow up**: 144/153 (94%) completed treatment. n=9 (3 Gp A, 6 Gp 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 Gp A, 65 Gp B and 9 Gp C). **Compliance**: n=9 discontinued treatment (1 Gp A, 6 Gp B, 2 Gp C). n=8 prematurely withdrew for non-safety reasons (1 Gp A, 5 Gp B, 2 Gp C).	

Definitions: Gp, group; ALT, alanine transaminase level; ULN, upper limit of normal; PCR, polymerase chain reaction assay; RVR, rapid virological response (defined as serum HCV RNA <600 IU/ml at 4 weeks of treatment); SVR, sustained virological response (defined as undetectable serum HCV RNA 24wks after end of treatment)

Outcome	**Gp A (n=71) 16wks, RVR**	**Gp B (n=71) 24wks, RVR**	**Gp C (n=11) 24wks, no RVR**
Viral Response, % (n/N)			
4 wk (RVR)	100%	100%	0
12 wk (EVR)	-	-	-
End of treatment	94% (67/71)	85% (60/71)	72%[b]
End of follow-up (SVR)	82% (58/71)[a]	80% (57/71)	36%[c]
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)[d]	-
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)	-
[a]difference of at most 11.5% (97.5% 1-sided CI) for Gp A vs B; [b]*p*=ns for Gp B vs C; [c]*p*=0.005 for Gp B vs C; [d]*p*>0.2 for Gp A vs B.			
Biochemical response, % (n/N)			
End of treatment	-	-	-
End of follow-up	89%	87%	67%
Histology			
Inflammation	not reported	not reported	not reported
Fibrosis			
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/lab abnormalities			
Peg IFN	5 (7.0%)	13 (18.8%)	4 (36.4%)
Ribavirin	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%)
dyspnea	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 1 dose of study medication.			

Additional Results/comments (e.g., early response factors, quality of life):

Virological response

- After first 4wks 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 pts and 1 pt 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 end of treatment response was achieved in 135/153 pts (88%), and an SVR in 119/153 pts (78%).

SVR according to genotype and pre-treatment viraemia

- SVR in genotype HCV-2 pts were higher than in HCV-3 pts (92% vs 73% respectively) *(no p value reported)*, and were not affected by pre-treatment viraemia. However, HCV-3 pts with a baseline

viraemia >800,000 IU/mL achieved a significantly lower SVR compared with pts with baseline viraemia ≤800,000 IU/mL (59% vs 85% respectively, *p*=0.003).
- There were no significant differences between groups A & B for SVR rates for pts with either HCV-2 or HCV-3.

Predictors of SVR
- From multivariate logistic regression analysis of all pts, genotype HCV-2, low viral load and low γ-glutamyltransferase (GGT) value were independent factors of SVR. Based on pts 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 pts without a rapid virological response (group C) compared with pts with rapid virological response (groups A & B); however, differences did not reach statistical significance.

Biochemical response
- Sustained biochemical response was observed in 110/115 sustained virologic responders (96%), whereas 5 sustained virologic responders did not show a biochemical response with ALT levels ranging up to 2.95 times the upper limit of normal. Each of the 5 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 IFN + RBV. In general, the frequency of AE was lower in group A compared with groups B and C (*Reviewer note: no statistical comparison reported*). Neutropenia (3%) and anaemia (6%) were the most common AE leading to dose modification.

Methodological comments:
Allocation to treatment groups: no details about the randomisation method were reported. Pts with a rapid virological response at week 4 of therapy were randomised 1:1 at week 8. Pts were stratified according to baseline viraemia (≤800,000 IU/mL vs >800,000 IU/mL) and treatment centre.
Allocation concealment: not reported.
Blinding: Patients randomised at wk 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 intention to treat: 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 rapid virological response group (not reported whether Gp A or Gp B). One patient with missing data at weeks 2 and 4 was allocated to Gp 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 Gp C vs Gps A & B (2.4 vs 1.6 and 1.6 respectively); also the proportion of genotype 3 patients was higher in Gp C vs Gps A & B (91% vs 72% and 73% respectively). Characteristics for Gp A vs B were comparable. No statistical comparison was presented.
Method of data analysis: The primary statistical analysis was the determination of a 1-sided 97.5% CI for the difference in SVR rates between treatment groups A and B. Fisher's exact test and χ^2 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 <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/drop-out: Numbers reported but reasons not fully reported.
Other: SVR rates reported for Gp B in text are not consistent. Top right paragraph on p.524 reports an SVR of 81% and end-of-treatment response of 84% for Gp B, but in the previous paragraph reported 80% and 85% respectively. Differences are possibly due to rounding of figures.

General comments
Generalisability: treatment-naïve 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 Gp A, Gp B and Gp C respectively) was low and all patients in Gps A & B had RVR at wk 4.
Inter-centre variability: not reported
Conflict of interests: the study was partly supported by the drug manufacturer (Roche).

Quality criteria for assessment (updated CRD guidance) **(answer yes/no/unclear)**

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, e.g. 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 drop-outs 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 intention to treat analysis? If so: - was this appropriate? - were appropriate methods used to account for missing data?	Yes Yes Yes

Appendix 7 List of excluded studies

The reasons for study exclusion were applied in the order given in the inclusion criteria worksheet (Appendix 4). Studies may have been excluded on more than one criteria 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(7):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 (R)) plus ribavirin (COPEGUS (R)) in randomised controlled clinical trials are replicated in the clinical practice setting. *J Hepatol* 2007;46(Suppl. 1).

Andriulli A, Mangia A, Iacobellis A, Ippolito A, Leandro G, Zeuzem S. Meta-analysis: the outcome of anti-viral therapy in HCV genotype 2 and genotype 3 infected patients with chronic hepatitis. *Aliment Pharmacol Ther* 2008;28(4):397-404.

Berg C, Goncales FL, Jr., Bernstein DE, Sette H, Jr., Rasenack J, Diago M *et al*. Re-treatment of chronic hepatitis C patients after relapse: efficacy of peginterferon-alpha-2a (40 kDa) and ribavirin. *J Viral Hepat* 2006;13(7):435-40.

Cervoni J, Richou C, Thevenot T, Di Martino V. Shortened Course of Therapy for Chronic Hepatitis C Genotype 1 (G1) Patients Developing Rapid Virological Response (RVR): Meta-Analysis of Randomized Controlled Trials (RCTs). *J Hepatol* 2009;50(Suppl. 1):S220-S221.

Condat B. Peginterferon alpha-2b plus ribavirine compared with interferon alpha-2 and ribavirine for the treatment of chronic hepatitis C: A randomized trial. *HEPATO-GASTRO* 2002;9(2):141-2.

Derbala M, Amer A, Bener A, Lopez AC, Omar M, El GM. Pegylated interferon-alpha 2b-ribavirin combination in Egyptian patients with genotype 4 chronic hepatitis. *J Viral Hepat* 2005;12(4):380-5.

Di Martino V, Richou C, Thevenot T, Sanchez-Tapias JM, Ferenci P. Modulations of Peg-Interferon Plus Ribavirin Duration According to Hcv-Genotype and Virologic Response at W4 and W12: Meta-Analyses of Rcts with Individual Data. *Hepatology* 2008;48(4):404A.

Grewal AS, Choudhary A, Bechtold ML, Puli SR, Othman MO, Roy PK. Peginterferon and ribavirin for treatment of hepatitis C and HIV co-infection: A meta-analysis of randomized controlled trials. *Gastroenterology* 2008;134(4, Suppl. 1).

Mohsen A, Norris S. Hepatitis C (chronic). *Clinical Evidence* 2007.

Moreno L, Quereda C, Moreno A, Perez-Elias MJ, Antela A, Casado JL *et al*. Pegylated interferon alpha 2b plus ribavirin for the treatment of chronic hepatitis C in HIV-infected patients. *AIDS* 2004;18(1):67-73.

Nunez M, Marino A, Miralles C, Berdun MA, Sola J, Hernandez-Burruezo JJ *et al*. Baseline serum hepatitis C virus (HCV) RNA level and response at week 4 are the best predictors of relapse after treatment with pegylated interferon plus ribavirin in HIV/HCV co-infected patients. *Journal of Acquired Immune Deficiency Syndromes* 2007;45(4):439-44.

Nunez M, Miralles C, Berdun MA, Losada E, Aguirrebengoa K, Ocampo A *et al*. Role of weight-based ribavirin dosing and extended duration of therapy in chronic hepatitis C in HIV-infected patients: The PRESCO trial. *Aids Research and Human Retroviruses* 2007;23(8):972-82.

Opravil M, Sasadeusz J, Cooper DA, Rockstroh JK, Clumeck N, Clotet B *et al*. Effect of baseline CD4 cell count on the efficacy and safety of peginterferon Alfa-2a (40KD) plus ribavirin in patients with HIV/hepatitis C virus co-infection. *J Acquir Immune Defic Syndr* 2008;47(1):36-49.

Perronne C, Carrat F, Banisadr F, Morand P, Lunel F, Rosenthal E *et al*. ANRS HC02-Ribavic: A randomized controlled trial of pegylated interferon alpha-2b plus ribavirin vs interferon alpha-2b plus ribavirin as primary treatment of chronic hepatitis C in HIV co-infected patients. *Hepatology* 2002;36(No. 4, Pt. 2):283A.

Poynard T, Schiff E, Terg R, Moreno Otero R, Flamm S, Schmidt W *et al*. Sustained viral response (SVR) is dependent on baseline characteristics in the re-treatment of previous alfa interferon/ribavirin (I/R) nonresponders (NR): Final results from the EPIC3 program. 43rd Annual Meeting of the European Association for the Study of the Liver (EASL), Milan, Italy April 23rd - 27th, 2008.

Rodriguez-Torres M, Rodriguez-Orengo JF, Rios-Bedoya CF, Fernandez-Carbia A, Gonzalez-Lassalle E, Salgado-Mercado R *et al*. Efficacy and safety of peg-IFN alfa-2a with ribavirin for the treatment of HCV/HIV co-infected patients who failed previous IFN based therapy. *J Clin Virol* 2007;38(1):32-8.

Sanchez-Tapias JM, Diago M, Escartin P, Enriquez J, Romero-Gomez M, Barcena R *et al*. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterology* 2006;131(2):451-60.

Sarrazin C, Schwendy S, Moller B, Dikopoulos N, Buggisch P, Encke J *et al*. Individualized treatment duration with peginterferon-alfa-2B and ribavirin for 24, 30 or 36 weeks in HCV genotype1-infected patients with undetectable HCV-RNA early during therapy (INDIV-2 STUDY). *J Hepatol* 2009;50(Suppl No 1):S236.

Schiff E, Poordad F, Jacobson I, Flamm S, Bacon B, Lawitz E *et al*. Boceprevir (B) combination therapy in null responders (NR): response dependent on interferon responsiveness. *J Hepatol* 2008;48(Suppl 2):S46.

Shiffman ML, Mansbach H, Hammond J, O'Neill M. The effect of complete and partial response at week 12 on sustained virologic response: Results from controlled trials in naive HCV genotype 1 patients treated with pegylated interferon and ribavirin. *Hepatology* 2007;46(4, Suppl. S):824A-5A.

Shire NJ, Welge JA, Sherman KE. Response rates to pegylated interferon and ribavirin in HCV/HIV co-infection: a research synthesis (Cochrane provisional abstract). *J Viral Hepat* 2007;14(4):239-48.

Slavenburg S, Weggelaar I, van Oijen MGH and Drenth JPH. Optimal length of antiviral therapy in patients with hepatitis C virus genotype 2 and 3: a meta-analysis. EASL 44th Annual Meeting, Copenhagen 22nd -26th April 2009.

Yoshida EM, Sherman M, Bain VG, Cooper CL, Deschenes M, Marotta PJ *et al*. Retreatment with Pegylated interferon alpha-2a and ribavirin in patients with chronic hepatitis C who have relapsed or not responded to a first course of peylated interferon-based therapy. *Can J Gastroenterol* 2009;23(3):180-4.

Yu ML, Dai CY, Huang JF, Hou NJ, Lee LP, Hsieh MY *et al*. A randomized, controlled, open-label study of peginterferon alfa-2A (40KD) (PEGASYS (R)) plus ribavirin (COPEGUS (R)) for 16 vs. 24 weeks in patients with genotype 2 hepatitis C infection. *Hepatology* 2006;44(4):267A.

Zoulim F. Treatment of patients with chronic hepatitis C who relapsed or did not respond to a previous treatment. *Gastroenterol Clin Biol* 2002;26(2):B225-B230.

Reason for exclusion: population

Berak H, Kolakowska-Rzadzka A, Wasilewski M, Kowalska J, Stanczak JJ, Bardadin K *et al*. Randomized, open label trial comparing efficacy and safety of pegylated interferon alfa 2b vs alfa 2b treatment of patients with chronic hepatitis C infected with non 2/3 genotypes - final analysis. *J Hepatol* 2007;46 (Suppl 1):S217-S218.

Brady DE, An JW, Lawitz EJ, Harrison S. Does Induction Pegylated Interferon Alfa-2B in Combination with Ribavirin Enhance the Sustained Response Rates in Patients with Genotype 1 and 4 Chronic Hepatitis C? Results from A Prospective, Randomized, Multi-Center, Open-Label Treatment Study. *Hepatology* 2008;48(4):402A.

Brandao C, Barone A, Carrilho F, Silva A, Patelli M, Caramori C *et al*. The results of a randomized trial looking at 24 weeks vs 48 weeks of treatment with peginterferon alpha-2a (40 kDa) and ribavirin combination therapy in patients with chronic hepatitis C genotype 1. *J Viral Hepat* 2006;13(8):552-9.

Dalgard O, Bjoro K, Ring-Larsen H, Verbaan H. Peginterferon alpha-2b and ribavirin for 14 or 24 weeks in patients with HCV genotype 2 or 3 and rapid virological response. The North-C trial. *J Hepatol* 2007;46 (Suppl 1):S57.

Dalgard O, Bjoro K, Ring-Larsen H, Bjornsson E, Holberg-Petersen M, Skovlund E *et al*. Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. *Hepatology* 2008;47(1):35-42.

Diago M, Crespo J, Olveira A, Perez R, Barcena R, Sanchez-Tapias JM *et al*. Clinical trial: pharmacodynamics and pharmacokinetics of re-treatment with fixed-dose induction of peginterferon alpha-2a in hepatitis C virus genotype 1 true non-responder patients. *Aliment Pharmacol Ther* 2007;26(8):1131-8.

Everson GT, Hoefs JC, Seeff LB, Bonkovsky HL, Naishadham D, Shiffman ML *et al*. Impact of disease severity on outcome of antiviral therapy for chronic hepatitis C: Lessons from the HALT-C trial. *Hepatology* 2006;44(6):1675-84.

Ferenci P, Laferl H, Scherzer TM, Maieron A, Gschwantler M, Brunner H *et al*. Customizing treatment with peginterferon alfa-2a (40kd) (PEGASYS (R)) plus ribavirin (COPEGUS (R))

in patients with HCV genotype 1 or 4 infection. Interim results of a prospective randomized trial. *Hepatology* 2006;44(4):336A.

Jacobson IM, Brown RS, Jr., Freilich B, Afdhal N, Kwo PY, Santoro J *et al*. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. *Hepatology* 2007;46(4):971-81.

Kamal SM, El Tawil AA, Nakano T, He Q, Rasenack J, Hakam SA *et al*. Peginterferon alpha-2b and ribavirin therapy in chronic hepatitis C genotype 4: impact of treatment duration and viral kinetics on sustained virological response. *Gut* 2005;54(6):858-66.

Kamal SM, El Kamary SS, Shardell MD, Hashem M, Ahmed IN, Muhammadi M *et al*. Pegylated interferon alpha-2b plus ribavirin in patients with genotype 4 chronic hepatitis C: The role of rapid and early virologic response. *Hepatology* 2007;46(6):1732-40.

Lagging M, Pedersen C, Rauning BM, Farkkila M, Langeland N, Morch K *et al*. Comparison of peginterferon alpha-2a and ribavirin for 12 or 24 weeks in patients with HCV genotype 2/3: the Nordynamic trial. *J Hepatol* 2007;46 (Suppl 1):S229.

Lagging M, Pedersen C, Rauning BM, Färkkilä M, Langeland N, Mørch K *et al*. Peginterferon alfa-2A and ribavirin for 12 or 24 weeks in patients with HCV genotype 2/3: the Nordynamic trial. *Hepatology* 2007;46(4 Suppl 1):815A-6A.

Lagging M, Langeland N, Pedersen C, Farkkila M, Buhl MR, Morch K *et al*. Randomized comparison of 12 or 24 weeks of peginterferon alpha-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection. *Hepatology* 2008;47(6):1837-45.

Mangia A, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M *et al*. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2005;352(25):2609-17.

Mangia A, Minerva N, Carretta V, Bacca D, Ricci GL, Vinelli F *et al*. Predictors of rapid virologic response (RVR) in HCV genotype 1 chronic infected pts: Results of a randomized controlled trial on individualized treatment. *Hepatology* 2006;44(4, Suppl. 1):606A-7A.

Manns M, Zeuzem S, Sood A, Lurie Y, Cornberg M, Klinker H *et al*. Reduced dose and duration of peginterferon alfa-2B + weight-based ribavirin in European and Asian genotype 2 and 3 chronic hepatitis C patients (REDD 2/3 trial). *J Hepatol* 2009;50(Suppl No. 1):S59.

Mathew A, Peiffer LP, Rhoades K, McGarrity T. Sustained viral response to pegylated interferon alpha-2b and ribavirin in chronic hepatitis C refractory to prior treatment. *Dig Dis Sci* 2006;51(11):1956-61.

Mecenate F, Barbaro G, Pellicelli A, Barlattani A, Mazzoni E, Bonaventura M *et al*. Comparison of peginterferon alfa-2a and ribavirin for 12 or 24 weeks in patients with HCV genotype 2 or 3: the CLEO trial. *Hepatology* 2007;46(4 Suppl 1):828A.

Rumi M, Aghemo A, Prati GM, D'Ambrosio R, Donato MF, Russo A *et al*. Randomized Study Comparing Peginterferon-Alfa2A Plus Ribavirin and Peginterferon-Alfa2B Plus Ribavirin in Naive Patients with Chronic Hepatitis C: Final Results of the Milan Safety Tolerability (Mist) Study. *Hepatology* 2008;48(4):404A.

Sakai T, Iino S, Omata M, Kiyosawa K, Kumada H. Peginterferon alfa-2a (40KD) (PEGASYS (R)) plus ribavirin (COPEGUS (R)) in treatment-naive Japanese chronic hepatitis

C patients: efficacy and safety of a randomised, double-blind, multicentre, phase III trial. *J Gastroenterol Hepatol* 2006;21:A25.

Shiffman ML, Nelson DR, Hooper G, Messinger D, Zeuzem S. HCV Patients with genotype 2 or 3 who do not achieve a rapid virologic response (RVR) with peginterferon alfa-2a (40KD)(PEGASYS®) and ribavirin (COPEGUS®) are not easy to treat: an analysis of non-RVR patients from the ACCELERATE study. *Hepatology* 2007;46(4 Suppl 1):309A-10A.

Shiffman ML, Suter F, Bacon BR, Nelson D, Harley H, Sola R *et al*. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2007;357(2):124-34.

Shiha G, Abdel KE, Abbas B, Elshennawy H, Zalata KH. Sustained virological response of peginterferon alpha-2a plus ribavirin for chronic hepatitis C virus genotype 4. *J Hepatol* 2007;46 (Suppl 1):S215.

Siebert U, Sroczynski G, Aidelsburger P, Rossol S, Wasem J, Manns M *et al*. Clinical effectiveness and cost-effectiveness of tailoring chronic hepatitis C treatment with peginterferon alpha-2b plus ribavirin to HCV genotype and early viral response: a decision analysis based on German guidelines. *Pharmacoeconomics* 2009;27(4):341-54.

Tang KH, Herrmann E, Pachiadakis I, Paulon E, Tatman N, Zeuzem S *et al*. Clinical trial: individualized treatment duration for hepatitis C virus genotype 1 with peginterferon-alpha 2a plus ribavirin. *Aliment Pharmacol Ther* 2008;27(9):810-9.

Toyoda H, Kumada T, Kiriyama S, Sone Y, Tanikawa M, Hisanaga Y *et al*. Eight-week regimen of antiviral combination therapy with peginterferon and ribavirin for patients with chronic hepatitis C with hepatitis C virus genotype 2 and a rapid virological response. *Liver Int* 2009;29(1):120-5.

Tsubota A, Satoh K, Aizawa M, Takamatsu S, Namiki Y, Ohkusa T *et al*. Four-week pegylated interferon alpha-2a monotherapy for chronic hepatitis C with genotype 2 and low viral load: a pilot, randomized study. *World J Gastroenterol* 2008;14(47):7220-4.

Reason for exclusion: intervention

Behler CM, Vittinghoff E, Lin F, Chung RT, Peters MG, Robbins GK *et al*. Hematologic toxicity associated with interferon-based hepatitis C therapy in HIV type 1-coinfected subjects. *Clin Infect Dis* 2007;44(10):1375-83.

Cargnel A, Angeli E, Mainini A, Gubertini G, Giorgi R, Schiavini M *et al*. Open, randomized, multicentre italian trial on PEG-IFN plus ribavirin versus PEG-IFN monotherapy for chronic hepatitis C in HIV-coinfected patients on HAART. *Antivir Ther* 2005;10(2):309-17.

Carrat F, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, Benzekri A *et al*. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *JAMA* 2004;292(23):2839-48.

Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE *et al*. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-co-infected persons. *N Engl J Med* 2004;351(5):451-9.

Crespo M, Sauleda S, Esteban JI, Juarez A, Ribera E, Andreu AL *et al*. Peginterferon alpha-2b plus ribavirin vs interferon alpha-2b plus ribavirin for chronic hepatitis C in HIV-co-infected patients. *J Viral Hepat* 2007;14(4):228-38.

Dalgard O, Bjoro K, Ring-Larsen H, Verbaan H, North C. Is sustained virological response to HCV treatment associated with a clinical important improvement in vitality? *J Hepatol* 2008;48(Suppl 2):S272.

De Compadri P, Koleva D, Mangia A, Motterlini N, Garattini L. Cost minimisation analysis of 12 or 24 weeks of peginterferon alfa-2b + ribavirin for hepatitis C virus. *J Med Economics* 2008;11(1):151-63.

Di Bisceglie AM, Shiffman ML, Everson GT, Lindsay KL, Everhart JE, Wright EC *et al*. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. *N Engl J Med* 2008;359(23):2429-41.

Fuster D, Planas R, Gonzalez J, Force L, Cervantes M, Vilaro J *et al*. Results of a study of prolonging treatment with pegylated interferon-alpha2a plus ribavirin in HIV/HCV co-infected patients with no early virological response. *Antivir Ther* 2006;11(4):473-82.

Graham CS, Wells A, Liu T, Sherman KE, Peters M, Chung RT *et al*. Relationships between cellular immune responses and treatment outcomes with interferon and ribavirin in HIV/hepatitis C virus co-infection. *AIDS* 2006;20(3):345-51.

Haque M, Yoshida EM. Hepatitis C antiviral long-term treatment against cirrhosis (HALT-C) trial. *Ann Hepatol* 2009;8(1):78-9.

Hezode C, Foucher J, Bronowicki JP, Leroy V, Tran A, Larrey DG *et al*. Efficacy and Safety of An Intensified Regimen of Pegylated Interferon Alfa-2A Plus Ribavirin in HCV Genotype 1-Infected Patients Who Did Not Respond to A Prior Standard Regimen of Pegylated Interferon Alfa-2A Plus Ribavirin: An Interim Analysis of the Multicentric, Randomized, Controlled SYREN Trial. *Hepatology* 2008;48(4 Suppl.):1148A-9A.

Jensen D, Craxi A, Brandao-Mello C, Di Bisceglie A, Andreone P, Freilich B *et al.* Identifying patients with a high likelihood of achieving an SVR following re-treatment with peginterferon alfa-2a (40KD) plus ribavirin: use of positive prognostic factors (PPF'S). *J Hepatol* 2009;50(Suppl No 1):S228.

Jensen DM, Marcellin P, Freilich B, Andreone P, Di BA, Brandao-Mello CE *et al*. Re-treatment of patients with chronic hepatitis C who do not respond to peginterferon-alpha 2b: a randomized trial. *Ann Intern Med* 2009;150(8):528-40.

Kallinowski B, Stein K, Boecher W, Goeser T, Spengler U, Link R *et al*. Comparison of a shortened ribavirin treatment vs a 24 week standard combination therapy in HCV infected patients with genotype 2/3. *J Hepatol* 2007;46 (Suppl 1):S228-S229.

Khalili M, Bernstein D, Lentz E, Barylski C, Hoffman-Terry M. Pegylated interferon alpha-2a with or without ribavirin in HCV/HIV co-infection: partially blinded, randomized multicenter trial. *Dig Dis Sci* 2005;50(6):1148-55.

Kim AI, Dorn A, Bouajram R, Saab S. The treatment of chronic hepatitis C in HIV-infected patients: a meta-analysis. *HIV Med* 2007;8(5):312-21.

Laguno M, Murillas J, Blanco JL, Martinez E, Miquel R, Sanchez-Tapias JM *et al*. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. *AIDS* 2004;18(13):F27-F36.

Laguno M, Larrousse M, Murillas J, Blanco JL, Leon A, Milinkovic A *et al*. Predictive value of early virologic response in HIV/hepatitis C virus-coinfected patients treated with an interferon-based regimen plus ribavirin. *J Acquir Immune Defic Syndr* 2007;44(2):174-8.

Laguno M, Cifuentes C, Murillas J, Veloso S, Larrousse M, Payeras A *et al*. Randomized trial comparing pegylated interferon alpha-2b versus pegylated interferon alpha-2a, both plus ribavirin, to treat chronic hepatitis C in human immunodeficiency virus patients. *Hepatology* 2009;49(1):22-31.

Lissen E, Clumeck N, Sola R, Mendes-Correa M, Montaner J, Nelson M *et al*. Histological response to pegIFNalpha-2a (40KD) plus ribavirin in HIV-hepatitis C virus co-infection. *AIDS* 2006;20(17):2175-81.

Marcellin P, Freilich B, Andreone P, DiBisceglie A, Brandao CE, Reddy KR *et al*. HCV-RNA status at week 12 of treatment with peginterferon alfa2a/RBV predicts SVR in patients with prior non-response to pegylated interferon alfa-2b/RBV: results from repeat study. *J Hepatol* 2008;48(Suppl 2):S301.

Marcellin P, Freilich B, Andreone P, DiBisceglie A, Brandao CE, Reddy KR *et al*. Type of response to prior pegylated interferon alfa-2B (12KD)/RBV predicts subsequent response to retreatment with peginterferon alfa-2A (40KD)/RBV. *J Hepatol* 2008;48(Suppl 2):S306.

Puoti M, Zanini B, De LA, Quinzan GP, Allegri R, Bruno R *et al*. Results of a randomized controlled trial on the impact of prolonged combination anti-HCV treatment in HIV/HCV co-infected patients. *J Hepatol* 2008;48(Suppl 2):S309.

Rodriguez-Torres M, Torriani F, Rockstroh J, DePamphilis J, Carosi G, Dieterich DT. Patients co-infected with HCV and HIV who achieve an RVR (HCV RNA <50 IU/mL at week 4) or cEVR (HCV RNA <50 IU/mL at week 12) have similar rates of SVR to monoinfected patients treated with peginterferon alfa-2a (40KD) (PEGASYS®) and ribavirin (COPEGUS®). *Hepatology* 2007;46(4 Suppl 1):814A.

Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A *et al*. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004;351(5):438-50.

Zhao S, Cheng D, Liu E, Yu H, Yang H, Xue X *et al*. Peginterferon vs. interferon in the treatment of different HCV genotype infections in HIV patients. *Eur J Clin Microbiol Infect Dis* 2008;27(12):1183-92.

Reason for exclusion: outcomes

Shiffman ML, Morishima C, Lindsay KL, Hoefs JC, Dienstag JL, Szabo G *et al*. Suppression of serum HCV RNA levels during maintenance peginterferon (pegifn) alfa-2a therapy and clinical outcomes in the HALT-C trial. *J Hepatol* 2008;48(Suppl 2):S62.

Appendix 8 SVR estimates for re-treated, and for HCV/HIV co-infected patients used in the SHTAC economic model

Re-treated patients

As explained in Section 3.3 of this report, no RCTs of re-treatment with peginterferon alfa and ribavirn 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 best supportive care 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 α-2a and ribavirin) (Jensen and colleagues[87]). For the purposes of economic modelling we have used the SVR reported for Group C of the trial (peginterferon α-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 α-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 (Poynard and colleagues)[94] which was also used by Schering-Plough in their submission to NICE. EPIC3 is an uncontrolled study which 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 best supportive care will 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 anti-viral 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 and ribavirin was compared to either peginterferon alfa monotherapy or to non-peginterferon alfa and 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 best supportive care (as explained in Section 3.3) we have assumed that no patients receiving only best supportive care 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	**Number with SVR (%)**	**Total number patients**
Peginterferon α-2a		
Chung et al (2004) [119]	18 (27)	66
Torriani et al (2004)[66]	116 (40)	289
Combined	**134 (38)**	**355**
Peginterferon α-2b		
Carrat et al (2004)[120]	56 (27)	205
Laguno et al (2004)[93]	23 (44)	52
Crespo et al (2007)[121]	33 (55)	60
Cargnel et al (2005)[122]	15 (22)	69
Combined	**127 (33)**	**386**

Genotype 1 / 4

Study	**Number with SVR (%)**	**Total number patients**
Peginterferon α-2a		
Chung et al (2004) [119]	7 (14)	51
Torriani et al (2004)[66]	57 (30)	194
Combined	**64 (26)**	**245**
Peginterferon α-2b		
Carrat et al (2004)[120]	21 (17)	125
Laguno et al	12 (38)	32

Crespo et al (2007)[121]	18 (46)	39
Cargnel et al (2005)[122]	4 (11)	37
Combined	**55 (24)**	**233**

Genotype 2 / 3

Study	**Number with SVR (%)**	**Total number patients**
Peginterferon α-2a		
Chung et al (2004) [119]	NA	NA
Torriani et al (2004)[66]	59 (62)	95
Combined	**59 (62)**	**95**
Peginterferon α-2b		
Carrat et al (2004)[120]	35 (44)	80
Laguno et al	10 (57)	19
Crespo et al (2007)[121]	15 (71)	21
Cargnel et al (2005)[122]	11 (34)	32
Combined	**71 (47)**	**152**

Data for the Cargnell and colleagues study have been added in, but these were not used in the respective meta-analyses of peginterferon alfa and ribavirin compared to 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 for G1/4 patients was not used in the meta-analysis by Kim and colleagues, 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 9 Variables and probability distributions used in the probabilistic model

Name	Distribution	alfa	beta
Transition probabilities			
Mild to moderate chronic HCV	Beta	38.08594	1485.35156
Moderate chronic HCV to compensated cirrhosis	Beta	26.90504	700.25822
Compensated cirrhosis to decompensated cirrhosis	Beta	14.61681	360.17319
Compensated cirrhosis to HCC	Beta	1.93256	136.10744
Decompensated cirrhosis to HCC	Beta	1.93256	136.10744
Decompensated cirrhosis excess mortality	Beta	147.03000	983.97000
HCC excess mortality	Beta	117.10333	155.23000
Utilities			
Utility of SVR (from mild chronic HCV)	Beta	65.86776	14.45878
Utility of SVR (from moderate chronic HCV)	Beta	58.06080	22.57920
Utility of SVR (from compensated cirrhosis) - by assumption	Beta	58.04760	37.11240
Utility of mild chronic HCV	Beta	521.23750	155.69432
Utility of moderate chronic HCV	Beta	168.24614	86.67226
Utility of compensated cirrhosis	Beta	47.10208	38.53806
Utility of decompensated cirrhosis	Beta	123.75000	151.25000
Utility of hepatocellular carcinoma	Beta	123.75000	151.25000
Utility of liver transplant	Beta	123.75000	151.25000
Utility of post liver transplant	Beta	59.25480	29.18520
Health state costs			
Cost of SVR state	Gamma	28.81409	8.98866
Cost of mild chronic HCV	Gamma	25.69952	5.36975
Cost of moderate chronic HCV	Gamma	88.85025	8.06976
Cost of compensated cirrhosis	Gamma	24.23423	46.95836
Cost of decompensated cirrhosis	Gamma	36.03281	253.13041
Cost of hepatocellular carcinoma	Gamma	18.10811	448.80449
Cost of liver transplant	Gamma	89.75357	304.50042
Cost of care in year in which liver transplant occurs	Gamma	13.77880	686.41683
Cost of care in years after liver transplant occurs	Gamma	15.21890	91.00529

Treatment effects	distribution	events	population
Shortened treatment duration peginterferon α-2a			
Liu et al[53]			
SVR – standard duration	Beta	57	58
SVR – shortened duration	Beta	69	74
Yu et al, 2007[54]			
SVR – standard duration	Beta	24	25
SVR – shortened duration	Beta	27	29
Yu et al, 2008[55]			
SVR – standard duration	Beta	85	88
SVR – shortened duration	Beta	43	44
Yu et al, 2007[54]			
SVR – standard duration	Beta	27	31
SVR – shortened duration	Beta	33	35
Shortened treatment duration peginterferon α-2b			
SVR – standard duration	Beta	8	19
SVR – shortened duration	Beta	16	28
Re-treatment with peginterferon α-2a			
EVR – genotype 1	Beta	21	142
SVR – genotype 1	Beta	18	21
EVR – non genotype 1	Beta	10	29
SVR – non genotype 1	Beta	6	10
Re-treatment with peginterferon α-2b			
EVR – genotype 1	Beta	333	1121
SVR – genotype 1	Beta	162	333
EVR – non genotype 1	Beta	162	206
SVR – non genotype 1	Beta	117	162
HCV/HIV co-infected treated with peginterferon α-2a			
SVR – genotype 1+4	Beta	64	245
SVR – genotype 2+3	Beta	59	95
HCV/HIV co-infected treated with peginterferon α-2b			
SVR – genotype 1+4	Beta	55	233
SVR – genotype 2+3	Beta	71	152