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Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C in children and young people

Assessment Report

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The clinical and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C in children and young people

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Contribution of authors

D Hartwell (Senior 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; K Cooper (Senior Research Fellow, Health Economics) developed the research protocol, assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, developed the economic evaluation, drafted the report; GK Frampton (Research Fellow) contributed to the background section, assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence and drafted the report; L Baxter (Research Fellow, Health Economics) assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, assisted in developing the economic evaluation, drafted the report; E Loveman (Senior Research Fellow) contributed to developing the research protocol, drafted 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 the report, acted as guarantor for the project.

ABSTRACT

Objectives: To assess the clinical effectiveness and cost-effectiveness of peginterferon α-2a and peginterferon α-2b in combination with ribavirin, within their licensed indications, for the treatment of chronic hepatitis C virus (HCV) in children and young people aged 3 to 17 years.

Data sources: Twelve electronic bibliographic databases, including the Cochrane library, MEDLINE and EMBASE, were searched up to November 2012. Bibliographies of retrieved papers, key hepatitis C websites and symposia and manufacturers' submissions to the National Institute for Health and Clinical Excellence (NICE) were also searched, and clinical experts were contacted.

Review methods: Systematic reviews of clinical effectiveness and cost-effectiveness were conducted, including studies of HRQoL, following standard guidelines to ensure methodological rigour. Clinical effectiveness studies were included if they were in children and young people aged 3 to 17 years with chronic compensated HCV of any severity, including those with HIV co-infection and those who were treatment naïve or had been previously treated. Eligible interventions were peginterferon α-2a or peginterferon α-2b, each in combination with ribavirin, compared against best supportive care (BSC) or against each other, and study designs were randomised or non-randomised controlled trials or uncontrolled cohort studies. Outcomes included sustained virological response (SVR) and adverse events. Previously published Markov state-transition economic models of chronic HCV in adults were adapted to estimate the cost-effectiveness of peginterferon α-2a and peginterferon α-2b (in combination with ribavirin) compared to BSC in children, and one another. The model extrapolated the impact of SVR on life expectancy, quality-adjusted life expectancy and lifetime costs. Uncertainty was explored through probabilistic and deterministic sensitivity analyses.

Results: Seven studies (two peginterferon α-2a and ribavirin and five peginterferon α-2b and ribavirin) were included in the review of clinical effectiveness. Six were single-arm cohort studies and one was an RCT for which only data for a single arm met the inclusion criteria. Overall, the studies were relatively small and of generally poor quality. SVR rates ranged from 53-66% (peginterferon α-2a) and 29-75% (peginterferon α-2b) (49-65% if excluding two studies with very small sample sizes). Rates of non-response and relapse were variable and adverse events were generally mild. No studies of cost-effectiveness or HRQoL in children and young people met the inclusion criteria. HRQoL, utilities and costs of treatment were therefore taken from studies on adults with chronic HCV. From this model, peginterferon alfa (α-2a or α-2b) in combination with ribavirin was more effective and cheaper than BSC. Peginterferon α-2a was slightly cheaper with higher QALYs than peginterferon α-2b, therefore peginterferon α-2b was dominated by peginerferon α-2a. Results were robust to changes in the sensitivity analyses.

Conclusions: Treatment of children and young people with peginterferon (α-2a or α-2b) and ribavirin may be an effective therapy. Results from the independent Markov model suggest that peginterferon (α-2a or α-2b) in combination with ribavirin is cost-effective compared with BSC, and peginterferon

α-2a is more cost-effective than peginterferon α-2b. However, the available evidence is of poor quality.

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Background

The hepatitis C virus (HCV) in children and young people is most commonly acquired via vertical transmission where the virus is passed down from an HCV-infected mother to her child in the perinatal period. The prevalence of HCV in children of all ages is unclear and difficult to establish but estimates are in the region of 0.1% to 0.4%. Progressive liver disease, as a result of chronic HCV infection, usually develops slowly over a number of years, often decades. Spontaneous viral clearance may occur early in the history of infection in young children, but once established chronic HCV tends to persist into adult life. Many children and young people will have mild disease with few obvious signs and symptoms of infection, although a small proportion of children with chronic HCV will develop significant liver disease during childhood. Quality of life (QoL) may be affected and some may experience the burden of social stigma. The National Institute for Health and Clinical Excellence (NICE) have previously recommended the use of peginterferon alfa (peginterferon α) and ribavirin combination therapy in adults with chronic HCV in the UK. Optimal therapy for children is less clear but it has been suggested that they should be treated using the same principles applied to the treatment of adults. Successful treatment is considered to be attainment of a sustained virological response (SVR), defined as undetectable serum HCV ribonucleic acid (RNA) levels six months after treatment cessation. The marketing authorisations for the two available brands of peginterferon (peginterferon α-2a and peginterferon α-2b) have either been extended to allow children and young people to also receive treatment, or will be extended shortly. This review focuses specifically on these new indications.

Objectives

To assess the clinical effectiveness and cost-effectiveness of peginterferon α-2a and peginterferon α-2b in combination with ribavirin, within the licensed indications, for the treatment of chronic HCV in children and young people aged 3 to 17 years.

Methods

Clinical effectiveness

A search strategy was developed and applied to 12 electronic bibliographic databases (including the Cochrane library, MEDLINE and EMBASE) from database inception to November 2012. Bibliographies of retrieved papers were screened, general and key hepatitis C websites and symposia were searched, and experts were also contacted to identify any additional published and unpublished references. Manufacturers' submissions to NICE were also searched.

Titles and abstracts (where available) were screened for potential eligibility by two reviewers independently using inclusion criteria that were defined *a priori*. Screening of the full text of retrieved papers was performed by one reviewer and checked by a second. Studies were eligible for inclusion if the participants were children and young people aged 3 to 17 years with compensated chronic HCV of any severity, including those with HIV co-infection and those who were treatment naïve or had been previously treated. Randomised controlled trials (RCTs) and non-RCTs were eligible for inclusion; uncontrolled studies were considered in the absence of any controlled studies. Data extraction and assessment of methodological quality were undertaken by one reviewer and checked by a second. Differences in opinion were resolved through discussion at each stage or consultation with a third reviewer if necessary. Data were synthesised through a narrative review with tabulation of the results of included studies. It was not considered appropriate to combine the studies in a meta-analysis primarily due to study design and poor study quality.

Cost-effectiveness

A systematic review of economic evaluations of peginterferon alfa for children was conducted using standard methods for evidence synthesis. Manufacturers' submissions to NICE were also reviewed. We adapted our previously published economic models of chronic HCV in adults to estimate the cost-effectiveness of peginterferon α-2a and peginterferon α-2b (in combination with ribavirin) compared to best supportive care (BSC), and one another, in children. The Markov cost-effectiveness model included health states for progression between chronic HCV health states and the more severe disease states of decompensated cirrhosis, hepatocellular carcinoma and liver transplant. Patients who responded to treatment achieved an SVR. The model extrapolated the impact of SVR on life expectancy, quality-adjusted life expectancy and lifetime costs. A systematic review of health related quality of life (HRQoL) for patients with hepatitis C was conducted and utility values extracted from the identified studies were used to derive the quality-adjusted life years (QALYs) associated with each treatment strategy. Resource use assumptions were adopted from our previously published models for adults with hepatitis C. 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 adult patients with chronic HCV and other published sources were used. Costs and benefits were discounted at 3.5% per annum. The perspective of the cost-effectiveness analysis was that of the NHS and personal social services. Uncertainty was explored through deterministic and probabilistic sensitivity analysis.

Results

Clinical effectiveness

A total of 811 references were identified after de-duplication. Seven studies (reported in 16 publications) were included in the review of clinical effectiveness, of which two evaluated peginterferon α-2a and ribavirin, and five evaluated peginterferon α-2b and ribavirin. Six of the included studies were single-arm, uncontrolled cohort studies and one was an RCT for which only data for a single arm met the inclusion criteria. No studies were identified that compared peginterferon alfa and ribavirin to BSC, nor peginterferon α-2a versus peginterferon α-2b. On the whole, the cohort studies were relatively small and of generally poor quality.

SVR rates ranged from 53-66% in children treated with peginterferon α-2a and 29-75% for those treated with peginterferon α-2b. The two peginterferon α-2b studies at the extremes of this range had very small participant numbers (n=7, n=12) which may raise a question over the reliability of the data. If these two studies are excluded, the SVR for peginterferon α-2b ranged from 49-65%.

Secondary outcomes were not always reported by all the studies. In five studies (two peginterferon α-2a and three peginterferon α-2b), children with genotype 2 or 3 appeared to have higher SVR rates than those with genotype 1, and three studies (two peginterferon α-2a and one peginterferon α-2b) found that children with low viral load at baseline achieved higher SVR rates compared to those with high viral load. In two peginterferon α-2b studies, children who were treatment naïve were more likely to achieve an SVR than those who had been previously treated. It should be noted that numbers of children in some of these subgroups were very small and none of the studies was statistically powered for subgroup analysis, therefore results should be interpreted with caution.

Rates of non-response were variable, ranging from 12-25% (two peginterferon α-2a studies) and 17-51% (three peginterferon α-2b studies). A relapse rate of 17% was reported by one peginterferon α-2a study and a range of 3-17% across four peginterferon α-2b studies. Adverse events were not consistently reported across all the studies but generally appeared typical of those associated with peginterferon and ribavirin and included flu-like symptoms, headache, gastrointestinal symptoms and anaemia. The incidence of dose discontinuation due to adverse events was relatively low and ranged from 3-7% (two peginterferon α-2a studies) and 1-10% (two peginterferon α-2b studies). The rate of dose modifications was variable and inconsistently reported. Adverse events leading to dose modification were usually anaemia and neutropenia. There was very limited data on QoL and growth. In one peginterferon α-2a study, most children showed no clinical changes in any of the measures of QoL. The impact on growth was often presented only in a brief narrative so no firm conclusions can be drawn.

Cost-effectiveness

The systematic review of published economic evaluations identified two cost-effectiveness studies for the treatment of children with antiviral therapy but neither of these met the inclusion criteria. The systematic review of HRQoL in children with hepatitis C did not identify any relevant studies. An update of HRQoL in adults found one new study and one previously unidentified study that provided EQ-5D utility values for patients with chronic HCV.

Two manufacturers submitted evidence to be considered:

Merck Sharp and Dohme (MSD), the manufacturer of peginterferon α-2b, constructed a lifetime Markov model with a model structure based upon that developed for previous NICE appraisals for adults. The model used the effectiveness of the treatments from a meta-analysis of the clinical trials. The base case results from the submission found that both combinations of peginterferon alfa dominated BSC in all age and genotype subgroups. There were small differences in costs and health outcomes between peginterferon α-2a and peginterferon α-2b. Peginterferon α-2b dominated peginterferon α-2a for most age and genotype subgroups.

Roche, the manufacturer of peginterferon α-2a, also constructed a Markov model based upon that developed for previous NICE appraisals for adults, with a time horizon of 30 years. The model used the effectiveness of peginterferon α-2a from a weighted average of four clinical trials. The base case results from the submission found that peginterferon α-2a is a cost-effective option for the treatment of paediatric HCV compared to BSC. Roche did not assess peginterferon α-2a compared with peginterferon α-2b.

In the independent Markov model, a time horizon of 70 years was used. The treatment effect was calculated using weighted averages taken from the studies included in the clinical effectiveness review. From this model, peginterferon alfa (α-2a or α-2b) in combination with ribavirin was more effective and cheaper than BSC. Peginterferon α-2a was slightly cheaper with higher QALYs than peginterferon α-2b, therefore peginterferon α-2b was dominated by peginerferon α-2a. Sensitivity analyses suggest that the results were generally robust to all changes to the structural assumptions and input parameters. The model results were most sensitive to changes to the discount rate, time horizon, SVR and baseline fibrosis of the cohort.

Discussion

The treatment of children and young people with peginterferon (α-2a or α-2b) and ribavirin may be an effective treatment, with SVR rates around 50-60%. However, the reliability of the available evidence is questionable given the single cohort study designs, small sample sizes and poor methodological quality.

The data available to populate the cost-effectiveness models was poor, and in many cases lacking altogether. For this reason, the models were largely based upon those previously developed for adults, assuming that these data would be appropriate and relevant for this population. Caution is therefore required in interpretation of the results.

The cost-effectiveness analyses submitted by the manufacturers were similar to that developed by the SHTAC independent model, with regard to model structure and data inputs, with all models largely based upon the previously developed model for adults. There were variations between the models for the time horizon chosen and the transition probabilities for progression between chronic HCV health states. The results from the cost effectiveness analyses submitted were consistent between the manufacturers' submissions and the SHTAC independent model.

This assessment was carried out following recognised guidelines and addresses a specific knowledge gap concerning the clinical and cost-effectiveness of peginterferon alfa and ribavirin treatment in children and young people with chronic HCV. In terms of limitations, there were a lack of good quality effectiveness data, and parameter values for the model had to be taken from the adult population since no suitable data for children and young people were identified.

Conclusions

Treatment of children and young people with peginterferon (α-2a or α-2b) and ribavirin may be an effective treatment. Results from the independent Markov model suggest that peginterferon (α-2a or α-2b) in combination with ribavirin is more effective and less expensive than BSC. However, the available evidence is of poor quality.

Implications for service provision

There are currently three specialised paediatric hepatology centres in the UK with well-established shared-care pathways. However, a recommendation for treatment with peginterferon alfa and ribavirin in children and young people with chronic HCV could potentially have implications for delivery of the service in terms of accessibility. The challenge for treating children and young people in more centres would be in making treatment accessible to all patients but with each centre treating enough patients to maintain expertise. Other implications include the need for more clinical nurse specialists and the additional burden on GP's, haematologists and child psychology services as a result of managing adverse effects.

Suggested research priorities

Well-conducted, head to head RCTs of peginterferon α-2a and ribavirin versus peginterferon α-2b are required, although it is unclear whether these are likely given the emergence of newer treatments. If

larger cohort studies were carried out, they should be statistically powered for the various subgroups in whom treatment response varies and be conducted in participants that reflect the chronic HCV paediatric population in the UK. Longer-term, more robust data are required to ascertain the long-term impact of peginterferon alfa treatment on the growth and QoL of children and young people with chronic HCV.

LIST OF ABBREVIATIONS

AE	Adverse events
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
DSA	Deterministic sensitivity analysis
EQ-5D	EuroQol-5 Dimension
EVR	Early virological response
EOT / ETR	End of treatment (virological response)
HAI	Histological activity index
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
HUI	Health Utility Index
HVL	High viral load
ICER	Incremental cost-effectiveness ratio
INB	Incremental net benefit
IU	International units
LVL	Low viral load
mcg, µg	Micrograms
ml	Millilitre
MS	Manufacturers' submission
MSD	Merck Sharp Dohme
NR	Not reported
NS	Not statistically significant
NICE	National Institute for Health and Clinical Excellence
PEG α	Peginterferon 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
RVR	Rapid virological response
SHTAC	Southampton Health Technology Assessments Centre
SF-36 / 6D	Short-form 36 or 6D
SG	Standard Gamble
SPC	Summary of product characteristics
SVR	Sustained virological response
TA	Technology Appraisal
TTO	Time Trade Off
ULN	Upper limit of normal
VAS	Visual Analogue Scale
wk	Week
WTP	Willingness to pay

1 BACKGROUND

1.1 Description of underlying health problem

Hepatitis C is a disease of the liver arising from the blood-borne hepatitis C virus (HCV). It is a slowly progressing disease which has two main phases of infection: acute and chronic. The period immediately after HCV infection is the acute phase. In some people, the virus will be cleared spontaneously during this phase, with the remaining developing chronic infection. Chronic HCV, defined as infection persisting for more than six months, is the focus of this assessment.

HCV is a ribonucleic acid (RNA) virus which has six genetic variations, known as genotypes. There are six major HCV genotypes (i.e. genotype 1, 2, 3, etc.), and within these there are several sub-types (labelled a, b, c, etc.). The prevalence of the genotypes varies considerably between countries, with the most prevalent groups in England and Wales being genotypes 1 and 3 (representing at least 90% of infections).[1-3] Of these, genotype 3a is the most common with a prevalence of 39%, followed by genotype 1a with a prevalence of 22%.[3] Response to treatment is strongly influenced by HCV genotype (see below).

Chronic HCV infection can be categorised as mild, moderate or severe according to the extent of damage to the liver. This is based on both the level of fibrosis (scarring) in the liver and the degree of inflammation and destruction of liver cells (necroinflammation) (discussed further in the *Diagnosis and Staging* section). Many children and young people with chronic HCV infection are asymptomatic although symptoms may occur later in the disease when liver damage has progressed.

Aetiology

HCV is acquired primarily through exposure to contaminated blood. In adults in the UK the most common source of infection is through the sharing of injecting equipment in intravenous drug misuse. This accounts for around 90% of cases.[3] Other sources of HCV infection include needle stick injury, tattooing and body piercing, and from treatment with contaminated blood products (prior to blood screening in 1991). The risk of sexual transmission is thought to be low.[3]

In children, mother-to-child ('vertical') transmission is the primary reason for HCV infection, with perinatal transmission being the most important route, and to a lesser extent, intrauterine transmission.[4;5] The rate of perinatal transmission from an HCV infected mother to her child ranges from 2% to 5%.[6;7] Breast feeding does not appear to increase the risk of HCV transmission, even though HCV RNA may be detected in breast milk and colostrum. A number of factors may change the risk of mother-to-child transmission. There is an increased risk of transmission depending on the

level of maternal viral load and whether the mother is also co-infected with human immunodeficiency virus (HIV).[8] A systematic review of 77 studies published in 2001 showed that the rate of mother-to-child transmission was in the region of 5% from women without HIV infection and 22.1% from women with HIV infection.[9]

Epidemiology

Estimates based on laboratory surveillance by the Health Protection Agency (HPA)[10] in the UK suggest that around 216,000 individuals were chronically infected with HCV in 2011. The prevalence of HCV in children of all ages is unclear and difficult to establish. The HPA report estimated that 26 children aged 1 year or below, 21 young people aged 1 to 14 years, and 439 people between the ages of 15 and 24 years were newly diagnosed with HCV in England in 2010. Many of the latter cases of HCV will be acquired through injecting drug use which often begins in late adolescence and early adulthood.[10]

Published population-based studies range in their estimates, in part owing to many studies having small, and in some cases, unrepresentative samples (e.g. antenatal screening can be selective), and thus vertical transmission may be undetected in some. Estimates generally suggest that the prevalence of HCV in children in developed countries is between 0.1% and 0.4%.[4;7;11] In some populations this may exceed 10% (e.g. in some regions of Saudi Arabia and Africa).[7] Estimates of regional prevalence rates in pregnant women in the UK range from 0.19% to 0.43%.[4] The prevalence of HCV genotypes in children is thought to be similar to that in adults given that the majority are infected by vertical transmission. Studies have shown that genotypes 1, 2 and 3 are the most clinically relevant groups in children with HCV, whilst genotype 4 is less prevalent.[7]

Progression and prognosis

The natural history of HCV acquired during childhood is not completely understood, although the age at onset of HCV infection is thought to be an important factor in the long-term outcome. In children, spontaneous viral clearance tends to occur early in the history of an infection and is more likely before the age of 4 years.[12] Once established, chronic HCV infection tends to persist into adult life, although the associated liver disease may be asymptomatic.[12] In vertical transmission, estimates suggest somewhere between 2.4% and 55% of children will spontaneously clear the infection, with the cumulative probability of progression to chronic HCV being approximately 80%.[4;7;12] Caution is required in the interpretation of these data however, as most of the studies that these estimates come from have small numbers of children, with different ages at acquisition of HCV and different co-morbidities.[4] Spontaneous viral clearance is thought to be dependent on genotype, with children infected with genotype 3 having a higher likelihood of clearance than those with genotype 1.[7;12]

Chronic HCV is a slowly progressing disease that usually develops over a number of years, often decades. The severity of chronic HCV relates to the duration of infection, meaning that progression to advanced disease is less likely in children than in adults.[11] A recent systematic review[6] evaluated the outcomes of untreated HCV in children from population based screening studies. Results from 25 studies including 733 people infected with HCV as children showed that of the 180 (25%) who underwent a liver biopsy as adults, only 4% had developed liver cirrhosis, with no other individuals developing any severe adverse outcomes. The authors concluded that the majority of people with disease acquired during childhood have a mild degree of hepatitis and fibrosis during childhood. No clear risk factors for severe adverse outcomes were identified in the studies reviewed. The review conclusions were limited by the relatively short follow-up periods in most of the studies included.[6] Other studies suggest that the rate of advanced liver fibrosis or cirrhosis seen on liver biopsy in children with chronic HCV infection is also relatively low, in the range of 2% to 6%.[7;11-15] According to clinical experts, no children have undergone liver transplantation due to chronic HCV infection in the UK. Despite the relatively innocuous nature of chronic HCV in children, clinicians believe that treatment during childhood is beneficial since a definitive resolution of disease may be achieved in a subgroup of patients, treatment may reduce children's social burden, and factors may be more favourable for a response. (e.g. a low viral load, less advanced disease).[7;16] In addition, clinical opinion suggests that children have fewer side effects of treatment than adults.

Some differences in outcomes between vertically-infected and parenterally-infected children have been found. For example, in young children vertical transmission may be associated with higher levels of alanine aminotransferase (ALT), an enzyme that may be elevated in concentration if damage to liver cells has occurred. Overall, however, the mode of infection appears to have a relatively limited impact on outcomes, which reflect a slowly progressing disease.[17;18]

Diagnosis and staging

The need for diagnostic testing in children is established by assessment of potential risk factors, such as HCV infection or drug use in the mother, or exposure to contaminated blood products or organ transplants. Diagnosis is undertaken using blood tests to detect HCV antibodies and to detect HCV RNA.[4] Identification of HCV antibodies uses enzyme linked immunosorbant assays (ELISA) or enhanced chemiluminescence tests, where test accuracy indices have been shown to be excellent.[19] In cases of suspected vertical transmission this testing procedure should ideally be undertaken after the child is older than 18 months, because maternal antibodies can cross the placenta and persist for up to 18 months, leading to potentially unreliable test results.[16]

A positive antibody test will be followed up with a test for the presence of HCV RNA in serum in order to determine active infection.[16;19] This is typically undertaken using a real-time polymerase

chain reaction (PCR) based test as these yield both sensitive and quantitative detection ranges. Recent clinical guidelines suggest that if undertaken in early infancy, a positive serum HCV RNA should be re-checked after 12 months of age to establish the presence of chronic HCV.[16] At this point the determination of positive HCV RNA may indicate acute or chronic infection, and the clinician will use patient history of the timing between the test and the likely exposure to aid diagnosis. If a test for HCV antibodies is positive but a test for HCV RNA is negative, this could indicate a resolved infection, and testing would be repeated after 6 months for confirmation.[4]

If chronic HCV infection is established, testing may be undertaken to establish the HCV genotype using a further PCR assay. In adults evidence has shown that HCV infections with viruses of genotypes 2 or 3 are the most likely to resolve with therapy, whilst infections with viruses of genotypes 1a or 1b are less likely to respond. The determination of the genotype is therefore an important and useful means to establish treatment options including the timing and duration of treatments, and once this is known this may be followed up with a liver biopsy to determine the extent of any liver fibrosis.[16;19] In children infected with the more responsive genotypes 2 or 3, treatments may commence without the need to test for the extent of liver fibrosis because the benefits of treatment are likely to outweigh the risks. In those with genotypes 1a and 1b however, the extent of liver fibrosis will be used to weigh up the benefits and risks of treating immediately versus waiting.[16] For some children who have been vertically infected the biopsy may be delayed until age 8 to 10 years as evidence of the natural history shows that fibrosis is unlikely to occur until at least this age.[19]

In children who have undergone a liver biopsy, chronic HCV infection may be classified as being mild, moderate or severe based on histological appearance. To determine the severity, two components of the liver biopsy sample are assessed: fibrosis (scarring) and necroinflammation.[20] The extent of fibrosis is expressed as a 'stage' ranging from no fibrosis to cirrhosis in its severe form. Cirrhosis can progress from a compensated state, where the liver is still functioning despite the fibrosis, to a decompensated state where the functioning of the liver is seriously impaired. The extent of necro-inflammation of the liver is expressed as a 'grade' of disease activity which relates to the rate at which the disease stage is changing. A weakness of the histological classification is that it does not differentiate the clinical process of decompensation (compensated or decompensated liver function can occur at the same stage of fibrosis or cirrhosis), so the fibrosis stage score may not necessarily increase as decompensation occurs. Inflammatory activity in the liver can increase or decrease, or remain constant, during the disease process.[20]

There are a number of commonly used systems for classifying liver biopsy samples. The three most commonly used are the Knodell Histological Activity index (HAI); The Ishak revised Histological Activity index (HAI), and the METAVIR system. Knodell and colleagues' system[21] comprises of four

components, one classifies the amount of fibrosis (scored from 0 [no fibrosis] to 4 [cirrhosis]) and three the extent of necro-inflammation (periportal and/or bridging necrosis; intralobular degeneration; and portal inflammation, with a combined maximum score of 18). The maximum combined score is therefore 22 where higher scores reflect more severe disease.

A revision of the HAI, primarily for use as a research tool, was published in 1995 by Ishak and colleagues.[22] The revised system applied five components. Four measure components of necro-inflammation grading: peri-portal or periseptal interface hepatitis, confluent necrosis, focal (spotty) lytic necrosis, apoptosis and focal inflammation, and portal inflammation, with a maximum score of 18. The fifth relates to fibrosis staging with a maximum score of six. The maximum score is therefore 24.

The METAVIR system was developed specifically for use in HCV and again scores the fibrosis stage and the necro-inflammation grade.[23] Fibrosis is scored from 0 to 4 from no fibrosis to cirrhosis or advanced scarring. Necro-inflammation is scored on a scale of 0 (no histological activity) to 3 (severe activity). The maximum score is therefore 7. The METAVIR system is the most widely used system in clinical trials of anti-viral treatment in chronic HCV and is considered to be the most validated instrument currently available.[20]

Impact of disease

Many children infected with HCV appear to be clinically asymptomatic or show only mild, non-specific symptoms (e.g. fatigue, flu-like symptoms, nausea).[6;7;16] As mentioned above (*Progression and prognosis* section), a small proportion of patients with chronic HCV will develop significant liver disease during their childhood. A retrospective study of 246 patients on the UK HCV National Register Database[13] found that when patients who were infected with HCV before age 16 reached their late teens some had started to show signs and symptoms of liver disease, including enlarged liver (43 patients), enlarged spleen (20 patients), visible blood vessel abnormalities (spider nevi; 4 patients), abdominal fluid retention (ascites) (3 patients), jaundice (3 patients), bleeding oesophageal varicose veins (varices) (1 patient) and itching (1 patient). Many of the patients on the database had comorbidities and, overall, those who developed signs and symptoms of liver disease were found to be statistically significantly more likely to have had underlying medical conditions in addition to HCV infection.[13] Another study based on medical records submitted by 12 paediatric and infectious diseases centres in Italy investigated outcomes for 504 children who were infected with HCV before age 16 but who did not have comorbid viral, autoimmune or metabolic disorders, haematological disorders, or malignancy.[12] The majority of children had non-specific, transient and mild symptoms at the time of diagnosis. However, six (1.8%) went on to develop signs and symptoms of advanced liver disease including weakness (asthenia), nosebleed, itching, ascites, and gastrointestinal bleeding, with

a mean duration of HCV exposure from putative time of exposure to diagnosis of cirrhosis of 9.9 years.[12] However, these data should be interpreted with caution, as they are from retrospective studies where the population selection and data capture are unclear. Transplant would be offered for children with end stage disease with significant complications of cirrhosis, including variceal bleeding and refractory ascites, or those with decompensated liver function (coagulopathy and encephalopathy) or those who develop hepatocellular carcinoma. However, these are rare in children with HCV infection without any other co-morbidity and, as mentioned above, no children in the UK are thought to have undergone liver transplantation due to chronic HCV.

Evidence from adult populations suggests that chronic HCV infection eventually leads to impairment in quality of life (QoL), even in the absence of liver inflammation, with patients feeling unwell in terms of both their physical and mental health.[24;25] However, information on the impact of infection with chronic HCV on children's QoL is very limited and it is difficult to draw clear conclusions from the available evidence. A small study on 19 HCV-infected children in Australia concluded that physical and psychosocial summary scores from validated self-reported and parent-reported questionnaires were significantly lower in infected compared to non-infected children. Children reported reduced physical functioning but were otherwise less concerned than their parents about future health.[26] Another study on 114 treatment naïve HCV-infected children used validated questionnaires to elucidate the behavioural, emotional and cognitive functioning of the children and their caregivers.[27] Children with HCV had significantly lower cognitive functioning scores than a normative sample, whilst some caregivers were found to be highly distressed by their children's medical circumstances, which limited family activities. However, the authors concluded that overall QoL was not impaired in children with chronic HCV infection.[27;28]

In adults, chronic infection with HCV is recognised as a social stigma[29] and it has been suggested that children chronically infected with HCV, and their families, experience the burden of social stigma,[8] although to date this does not appear to have been analysed quantitatively. According to clinical experts consulted during this technology assessment, parents often carry immense guilt, especially the mothers, if they have transmitted an HCV infection, and disclosing the diagnosis to their child can also be a huge burden. Children with HCV may experience stigma as a result of carrying an infection that they may later transmit; inappropriate segregation that can arise due to ignorance; and having a virus that may be perceived as related to negative social factors such as drug use and HIV.

Childhood infection with HCV has been estimated to increase the risk of liver-related death 26-fold.[30] There is a significant economic impact of paediatric HCV infection: projected 10-year costs associated with paediatric HCV infection in the USA (arising from the costs of screening, monitoring

and treatment) have been estimated at $199 to $335 million.[31] We are not aware of any cost data for the UK.

1.2 Current service provision

Treatment of chronic HCV is aimed at eradicating the virus and preventing related complications. Accordingly, the main goal of treatment is to clear HCV and achieve a sustained virological response (SVR), defined as undetectable HCV RNA in the serum at least six months after treatment ends. Successful treatment reduces the rate of progression of liver fibrosis and related complications and improves QoL for patients. Some baseline factors are known to be predictive of a greater likelihood of achieving an SVR, such as early virological response (EVR – measured 12 weeks after therapy commencement and defined as a negative HCV RNA [complete EVR] or a minimum 2 $\log_{10}$ drop in HCV RNA levels [partial EVR]). Other factors include genotype 2 or 3 (as stated previously), mild disease and low viral load.

Beyond the age of 4 years, most children and young people with chronic HCV are unlikely to clear the virus spontaneously and should be assessed for antiviral treatment. It is recommended that children diagnosed with HCV are referred to, and managed in conjunction with, a paediatric hepatologist at one of three specialised paediatric hepatology centres in the UK[4] – London, Birmingham or Leeds. Shared care pathways are well established in the UK, with treatment and overall care delivered outside the three specialist centres at joint clinics. Specialist hepatology nurses are also involved, particularly in the administration of antiviral treatment.

Optimal therapy for children with chronic HCV is not clearly defined due to the lack of efficacy data in children.[4;11] Published NICE technology appraisals[32-34] on the treatment of chronic HCV recommend treatment for any severity of disease but relate only to adults. There is currently no NICE guidance for the treatment of hepatitis C in patients younger than 18 years. The 2006 SIGN guidelines on the management of hepatitis C recommend that children with moderate or severe HCV should be considered for treatment with a combination of peginterferon and ribavirin, whilst the benefits of treatment for those with mild HCV should be weighed against the risk of treatment side effects.[35]

In current clinical practice in the UK, all children over 4 years of age are considered for treatment, with selection not based on histological severity. Treatment is rarely given to children under the age of 4 years as they may still clear the virus spontaneously. At older ages, treatment may take into account school stage (e.g. avoiding school examination years) where possible. In those with mild disease, which is the majority, the decision to treat is based on genotype and the likelihood of response. Children with genotypes that respond more favourably to treatment (genotypes 2 or 3) are

more likely to receive treatment, whilst those with genotypes 1 or 4 may receive a 'watchful waiting' approach, as long as there is no evidence of significant disease. Treatment of the minority who have severe disease is always considered more urgent, and treatment is more likely to be recommended. However, according to clinical expert opinion, it is rare for treatment of severe cases to be provided without considering the HCV genotype. Due to the lack of current guidance, there may be variation in practice between the three specialist centres in the UK. At some centres, biopsy would not be used in patients with HCV genotypes 2 or 3 but may be considered for genotype 1 if it would help guide the treatment decision. For patients keen to be treated, biopsy would not be performed whilst for patients preferring to wait, a biopsy may be deferred up to 10 years after infection.

For those children who are not treated, or where treatment is deferred, a best supportive care (BSC) approach is taken. A formal definition of BSC for children and young adults with chronic HCV is lacking. However, patients in this population are typically asymptomatic and it appears to be generally understood that BSC implies no active treatment. BSC may include watchful waiting, with six monthly reviews and monitoring of viral load and disease progression using blood tests for assessing HCV RNA or HCV antibodies and ultrasound scans every 1-2 years. The definition of BSC as comprising no active treatment is consistent with the NICE scope and the manufacturers' submissions and is the definition employed in our economic analysis (Chapter 5).

Two types of peginterferon alfa are available (see section 1.3), of which both are used in clinical practice in the UK, although the preferred form of the drug may vary between the treatment centres. The decision of when to treat is made on a case by case basis by the treating clinician in conjunction with the child/young person and/or their parent(s).

1.3 Description of technology under assessment

The intervention under review is dual therapy with peginterferon alfa (peginterferon α) and ribavirin. The peginterferons are cytokines whose mechanism of action is to assist the immune response by inhibiting viral replication. Two pharmacokinetically different forms[36] are available: peginterferon α-2a (Pegasys, Roche Products Ltd.) and peginterferon α-2b (ViraferonPeg, Merck Sharp & Dohme Ltd). Ribavirin (RBV) is a synthetic nucleoside analogue which is available in two primary forms, Copegus (Roche Products Ltd.) and Rebetol (Merck Sharp & Dohme Ltd.). It is also available as a number of generic forms, Ribavirin BioPartners (BioPartners GmbH), Ribavirin Mylan (Generics UK) and Ribavirin Teva (Teva Pharma B.V.). Copegus is indicated for combination therapy only with peginterferon α-2a, whilst Rebetol is indicated for combination therapy only with peginterferon α-2b.

Peginterferon α-2a was originally licensed in June 2002 and an extension to the licence to allow treatment in children and young people is expected shortly. In clinical practice, the dose used for children is 180mcg/1.73m^2 body surface area, once weekly, administered subcutaneously (an injection beneath the skin). Peginterferon α-2b was originally licensed in May 2000 with the most recent extension to the licence for use in children granted in February 2012. The recommended dose for children is 60mcg/m^2 body surface area, once weekly, administered subcutaneously. Treatment duration is recommended at 24 or 48 weeks dependent on genotype.

The two primary forms of ribavirin were licensed in November 2002 for Copegus (Roche Products) and May 1999 (oral tablets) and January 2005 (oral solution) for Rebetol (Merck Sharp & Dohme). The recommended dose of ribavirin is dependent on body weight and is 15 mg/kg/day for children and adolescents weighing <47 kg. It is taken each day in two divided doses as an oral solution.

For peginterferon α-2b, the most recent therapeutic indication is the treatment of children and adolescents aged three years and older with chronic hepatitis C, without liver decompensation, who are positive for serum HCV RNA and who have not previously been treated. The licence for peginterferon α-2a is anticipated to be indicated for the same group of children and adolescents but for those aged five years and older. The marketing authorisation for peginterferon α-2b does not permit peginterferon monotherapy in this age group and treatment must be given in combination with ribavirin. It is expected to be the same for peginterferon α-2a. Full details of the indications, dosages and duration of treatment are given in the Summaries of Product Characteristics.[37-40]

Clinical opinion suggests that, in the absence of any clear differences in clinical effectiveness, the choice of whether to use peginterferon α-2a or α-2b may depend on whether the drug is licensed, how easy it is to accurately measure the dose (since dosing in children is weight-based, requiring flexibility of dispensing), and local trust contracting arrangements (e.g. drug choice may be led by the adult service which treats a greater number of patients).

2 DEFINITION OF THE DECISION PROBLEM

This section states the key factors that will be addressed by this assessment in line with the definitions provided in the NICE scope.

There have been a number of technology appraisals by NICE of peginterferon and ribavirin for the treatment of adults with chronic hepatitis C, addressing mild (TA106[33]) and moderate to severe (TA75[32]) HCV, with the most recent appraisal in 2010 focusing on specific patient subgroups that were affected by licence extensions (TA200[34]). All of these appraisals were supported by independent

assessment reports conducted by SHTAC.[20;41;42] Since publication of these three technology appraisals, an additional extension to the licence for peginterferon α-2b has been granted, and an extension for peginterferon α-2a is undergoing consideration, to include those under the age of 18 years. The current health technology assessment relates specifically to the treatment of children and young people.

The interventions included within the scope of this assessment are (1) peginterferon α-2a in combination with ribavirin; and (2) peginterferon α-2b in combination with ribavirin. The population as defined by the NICE scope is children and young people aged 3 to 17 years with chronic HCV, and encompasses all groups including those with HIV co-infection; all grades of severity of chronic HCV (mild, moderate, severe); and those who are treatment naïve or, if appropriate, who have not responded and/or relapsed to previous treatments.

The relevant comparisons for this assessment are supportive care (including treatment without any form of interferon therapy), and the interventions compared with each other within their licensed indications. The outcomes under consideration include sustained virological response (HCV RNA levels 6 months after treatment cessation), virological response to treatment (e.g. HCV RNA levels at treatment week 12 or at the end of treatment), biochemical response (changes in ALT levels), liver inflammation and fibrosis, mortality, adverse effects of treatment including growth, and health-related quality of life. Fuller definitions of the outcomes are provided in section 4.2.

2.1 Overall aims and objectives of assessment

The aim of this health technology assessment is to review the clinical effectiveness and cost-effectiveness of peginterferon alfa (α-2a and α-2b) in combination with ribavirin, within the licensed indications, for the treatment of chronic HCV in children and young people. The objectives are:

- To undertake a systematic review of the clinical- and cost-effectiveness of peginterferon alfa in combination with ribavirin for children and young people with chronic HCV.
- To critique the manufacturer's submissions (MS) to NICE from Roche (Peginterferon α-2a) and Merck Sharp & Dohme (Peginterferon α-2b) to identify the strengths and weaknesses of the respective submissions.
- To develop an economic model to establish the cost-effectiveness of peginterferon alfa in combination with ribavirin for children and young people with chronic HCV.

3 METHODS

The methods for systematically reviewing the evidence of clinical- and cost-effectiveness were described *a priori* in a published research protocol (see Appendix 1). Peer review comments were sought from our clinical advisory group as well as from NICE. Minor amendments were made as appropriate but no comments that identified specific problems with the methods of the review were received. The methods of the economic evaluation are detailed in Chapter 5.

3.1 Identification of studies for the systematic reviews of clinical and cost-effectiveness

A search strategy was developed and refined by an experienced information specialist to identify all relevant studies investigating the two forms of peginterferon alfa with ribavirin in children and young people with chronic HCV. Separate searches were conducted to identify studies of clinical effectiveness, cost-effectiveness, resource use/costs, health-related quality of life (HRQoL) and epidemiology. The search strategies are provided in Appendix 2. Searches for clinical effectiveness and cost-effectiveness literature were undertaken from database inception to November 2012. The searches were not restricted by study design or language. The strategies were applied to the following databases:

- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Centre for Reviews and Dissemination (CRD) (University of York) databases: Database of Abstracts of Reviews of Effects (DARE), 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) and Conference Proceedings Citation Index - Science (CPCI) (ISI Web of Knowledge)
- BIOSIS Previews (ISI Web of Knowledge)

Bibliographies of retrieved papers were screened for relevant studies, and the MS to NICE were assessed for any additional studies. Members of the advisory group who were contacted for advice and peer review were also asked to identify any additional published and unpublished references. All search results were downloaded into a Reference Manager database (Thomson Reuters, New York, USA).

Other websites, including key hepatitis C websites and symposia, were also searched for completed or ongoing studies. These included: Clinical Trials.gov, Current Controlled Trials, UK Clinical Research Network Study Portfolio (UKCRN), Health Protection Agency (HPA), Food and Drug Administration (FDA), Department of Health (DoH), Zetoc, Scirus, Hepatitis C Trust, World Hepatitis Alliance, British Association for Study of the Liver (BASL), European Association for Study of the Liver (EASL), British Liver Trust, British Society of Gastroenterology (BSG), Foundation for Liver Research, American Association for Study of Liver Diseases (AASLD), Hepatitis C Scotland, Welsh Association for Gastroenterology and Endoscopy (WAGE), British Association for Liver Disease Nursing Forum (BASLNF), HIVandHepatitis.com, Cambridge Liver Symposium and the British Viral Hepatitis Group (BVHG).

3.2 Inclusion process

Each reference identified by the clinical effectiveness search strategy was screened for potential eligibility on the basis of title, and abstract (where available), using the inclusion criteria detailed below. Screening was carried out independently by two reviewers and the full texts of potentially relevant studies were obtained for further assessment. Screening of full papers was performed in a two-stage process. Firstly, papers were screened according to the inclusion criteria for population, intervention and outcomes using an inclusion coding sheet (Appendix 3). Papers that fulfilled these inclusion criteria were then screened on the basis of study design according to the hierarchy outlined in the *'Study design'* section below. It was not anticipated that there would be much randomised controlled trial (RCT) evidence in this population group and the two-stage process allowed an assessment of the different levels of evidence available whilst ensuring that all relevant studies were captured. Full papers were screened by one reviewer and checked by a second. At each stage, any disagreement between reviewers was resolved by discussion or involvement of a third reviewer where necessary.

Titles and abstracts identified by the cost-effectiveness search strategy were assessed for potential eligibility by two reviewers independently. Studies were only considered for inclusion if they reported the results of full economic evaluations (details below). Full papers of potentially relevant studies were retrieved and assessed for inclusion by two reviewers independently.

3.3 Inclusion and exclusion criteria

The following criteria reflect those stipulated in the final scope issued by NICE.

Population

Children and young people aged 3 to 17 years (peginterferon α-2b), or 5 to 17 years (peginterferon α-2a), with chronic HCV, without liver decompensation and who were positive for HCV RNA. All groups were considered, including:

- People with HIV co-infection
- People with all grades of severity of chronic hepatitis C (mild, moderate and severe)
- People who were treatment naïve or, if appropriate, people who had been previously treated but who relapsed or did not respond.

Interventions

- Peginterferon α-2a in combination with ribavirin
- Peginterferon α-2b in combination with ribavirin

Comparators

- Best supportive care (e.g. symptomatic treatment, monitoring, treatment without any form of interferon therapy)
- The interventions compared with each other within their licensed indications, i.e. peginterferon α-2a and ribavirin versus peginterferon α-2b and ribavirin

Outcomes

Studies had to report sustained virological response (SVR, defined as undetectable HCV RNA at least six months after treatment cessation). Studies could also include one or more of the following:

- virological response to treatment (e.g. during treatment, end of treatment)
- biochemical response (e.g. ALT)
- liver inflammation and fibrosis
- mortality
- adverse effects of treatment, including effects on growth
- HRQoL

Study design

- RCTs were included if available. If no RCTs of relevance were identified, non-randomised controlled trials were considered for inclusion. Studies without a control group were only considered for inclusion in the absence of any controlled studies.
- Studies published in the last five years (i.e. since 2007) as abstracts or conference presentations were only included if sufficient details were presented to allow an appraisal of the methodology and an assessment of results to be undertaken.
- For the systematic review of cost-effectiveness, studies were only included if they reported the results of full economic evaluations (cost-utility analyses, cost-effectiveness analyses [reporting cost per life year gained], cost-benefit analyses or cost-consequence analyses).
- Systematic reviews were only used as a source of references.
- Case series, case studies, narrative reviews, editorials and opinions were not included.
- Only studies published in the English language were included.

3.4 Data extraction strategy

Data from included clinical- and cost-effectiveness studies were extracted by one reviewer using a standardised and piloted data extraction form. Extracted data were checked by a second reviewer with any discrepancies resolved by discussion or recourse to a third reviewer when necessary.

3.5 Critical appraisal strategy

The quality of the clinical effectiveness studies was assessed according to criteria based on those used by the CRD (University of York).[43] The quality of the included economic evaluations was assessed using a critical appraisal checklist based upon those proposed by Drummond and colleagues[44] and Philips and colleagues.[45] Quality criteria of the included studies were assessed by one reviewer, and checked for agreement by a second reviewer. Any disagreements were resolved by consensus or consultation with a third reviewer if necessary.

3.6 Method of data synthesis

Clinical effectiveness data were synthesised through a narrative review with tabulation of the results of included studies. Full data extraction forms of all the included studies can be found in Appendix 4. It was not considered appropriate to combine the studies in a meta-analysis primarily due to study design and poor study quality, with the related uncertainties. There was also some heterogeneity between studies in patient characteristics (e.g. mode of HCV transmission, genotype mix, treatment history), all of which can have a potential impact on the virological response to treatment.

4 CLINICAL EFFECTIVENESS

4.1 Quantity and quality of research available

Literature searches identified 1384 references, with a total of 811 after removal of duplicates. Following the initial screening of titles and abstracts, 750 were excluded because they did not meet the specified inclusion criteria, and the full text of 61 articles was retrieved. Of these, 36 were excluded whilst 25 were further reviewed for possible inclusion. These were articles that met all of the inclusion criteria but had other factors to consider (e.g. the age of the participants exceeded the upper or lower limit without separate reporting of age-relevant subgroups). As such, nine of these articles were excluded after further inspection, leaving 16 included publications (seven studies). The total number of published papers included at each stage of the systematic review is shown in the flow chart in Figure 1, and the list of retrieved studies (with reasons for exclusion) can be seen in Appendix 5. The most common reason for exclusion was the wrong study population (many of the studies were in adults). A number of relevant abstracts were identified but were not included due to the insufficient reporting of methods and/or baseline data.

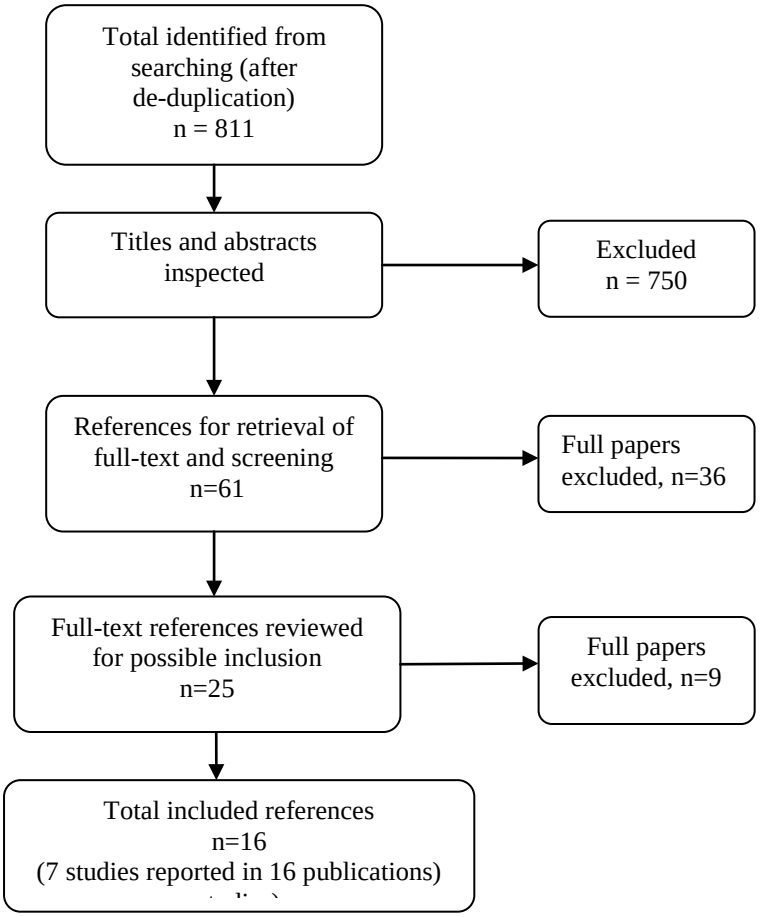


Figure 1 Flow chart for the identification of studies

Sixteen publications describing seven studies met the inclusion criteria of the review.[28;46-60] The nine additional publications were either abstracts[53;56;59] or linked articles[28;49-51;54;55] (e.g. reporting additional outcomes) to the main studies.[46-48;52;57;58;60] All of the included studies were single-arm, uncontrolled cohort studies, with the exception of one (Schwarz and colleagues[57]) which was an RCT. This was the pivotal license trial (known as PEDS-C) for peginterferon α-2a and ribavirin treatment in children and young people aged 5 to 18 years. The comparator arm in this trial was peginterferon monotherapy (peginterferon α-2a + placebo) which did not meet the inclusion criteria for the review (as based on the NICE scope for this appraisal[61]). Thus data for the intervention arm only could be used, effectively treating it as a single arm cohort study. One study[47] provided little aggregate data but fulfilled the inclusion criteria and has been included. Caution is suggested in interpreting data from this study and this is re-iterated in the results section. No studies were identified in children and young people with HIV co-infection.

The following section provides a description of the primary publications for the seven included studies[46-48;52;57;58;60] (Table 1).

Table 1 Studies included in the clinical effectiveness review

Author	Peginterferon type
Schwarz et al., 2011[57]	Peginterferon α-2a
Sokal et al., 2010[58]	Peginterferon α-2a
Al Ali et al., 2010[46]	Peginterferon α-2b
Pawlowska et al., 2010[52]	Peginterferon α-2b
Wirth et al., 2010[60]	Peginterferon α-2b
Ghaffar et al., 2009[47]	Peginterferon α-2b
Jara et al., 2008[48]	Peginterferon α-2b

Overview of the included studies

The key characteristics of the included studies are shown in Table 2. Two studies evaluated peginterferon α-2a and ribavirin[57;58] whilst five studies evaluated peginterferon α-2b and ribavirin.[46-48;52;60] The dose of peginterferon was administered subcutaneously once per week in all the studies, and was largely similar within peginterferon type. Peginterferon α-2a, given according to body surface area, was similar in the two studies (180µg/1.73m^2/week[57] [=104 µg/m^2/wk] and 100µg/m^2/week[58]), both with a maximum dosage of 180µg. The peginterferon α-2b dosage, given according to bodyweight, was 1.5µg/kg/week in three studies,[46;47;52] and Wirth and colleagues[60] reported that the dose of 60µg/m^2/week used in their study was equivalent to the licensed dose for adults of 1.5µg/kg/week. The study by Jara and colleagues[48] used a lower dose of 1.0µg/kg/week. Ribavirin was administered orally at a dose of 15mg/kg/day in all the studies, with the two

peginterferon α-2a studies stating a maximum dosage of 1200mg,[58] or 1200mg for bodyweight ≥75kg and 1,000mg for bodyweight <75kg.[57] Ribavirin is usually administered in two divided doses although this was explicitly stated in only three studies (one peginterferon α-2a,[57] two peginterferon α-2b[47;48]).

The duration of treatment was 48 weeks[46;57] or 52 weeks[47] in three studies (one peginterferon α-2a,[57] two peginterferon α-2b[46;47]), whilst two studies (one peginterferon α-2a,[58] one peginterferon α-2b[48]) treated participants for different durations according to genotype, which was generally 24 weeks for genotype 2 or 3 and 48 weeks for genotypes 1, 4, 5 or 6. The information provided by Pawlowska and colleagues[52] on treatment duration was not clear. They reported a duration of 48 weeks for all participants whilst also reporting that participants received 24 or 48 weeks of treatment according to genotype 2 and 3 or 1 and 4 respectively. Wirth and colleagues[60] also treated participants for different durations according to genotype but further divided those with genotype 3 according to baseline viral load, so that those with genotype 2 and those with genotype 3 and a low viral load received 24 weeks therapy, and those with genotype 1 or 4 and genotype 3 with a high viral load received 48 weeks of therapy.

All of the included studies were relatively small. The trial by Wirth and colleagues (peginterferon α-2b)[60] was the largest, recruiting 107 participants. The two peginterferon α-2a studies[57;58] and one peginterferon α-2b study[52] were similar in size with 53-65 participants (although Schwarz and colleagues[57] had n=55 for the peginterferon and ribavirin arm, with a total study size of N=114). The numbers of participants in the three smaller studies ranged from 7 to 30.[46-48]

Five of the studies (both peginterferon α-2a,[57;58] three peginterferon α-2b[48;52;60]) included participants with a mix of genotypes, although all consisted of a higher proportion of participants with genotype 1 (range 50-87%), or genotypes 1 or 4 (range 71-96%) compared to the other genotype subgroups. Participants with genotypes 2 or 3 accounted for only 3-25% of the included populations across the studies. The remaining two studies, both evaluating peginterferon α-2b, included only participants with genotype 4 (Al Ali and colleagues[46]), or largely genotype 4 where six of seven participants had genotype 4 and one was unknown (not tested) (Ghaffar and colleagues[47]). Over half of the studies included treatment naïve populations, with four (both peginterferon α-2a[57;58] and two peginterferon α-2b[46;60]) having 100% of participants not previously treated, and a fifth study (of peginterferon α-2b[48]) consisting largely of treatment naïve participants (80%). Ghaffar and colleagues[47] stipulated that one of seven children was previously treated whilst the treatment history of the other six children was not reported (so it is unclear whether they were treatment naïve or this was unknown). The study by Pawlowska and colleagues[52] (peginterferon α-2b) was conducted in a mixed population of treatment

naïve and previously treated (with non-pegylated interferon α-2b and ribavirin) in roughly equal proportions (54% and 46% respectively).

The age ranges of children included in the peginterferon α-2a studies (5-18 years) and peginterferon α-2b studies (3-17 years) are within those of the anticipated licence for peginterferon α-2a and the existing licence for peginterferon α-2b. Three of the peginterferon α-2b studies focused on a narrower age range, 8-17 years, which excluded young children.[46;47;52] The mean age was approximately 10-11 years in four studies (both peginterferon α-2a,[57;58] two peginterferon α-2b [48;60]) and older (14-16 years) in two peginterferon α-2b studies;[46;52] one peginterferon α-2b study[47] did not report mean age but the median was 10 years. The proportion of male participants was approximately half to two thirds of the total population in all studies except one (peginterferon α-2b[48]) (not reported). Vertical transmission was the most common mode of infection in four studies (both peginterferon α-2a,[57;58] two peginterferon α-2b[48;60]), accounting for nearly half the included population in one study[58] and around 70% in the other three.[48;57;60] Parenteral transmission was the most common route in the other three peginterferon α-2b studies,[46;47;52] ranging from 42% to 100%, and included infection via intravenous drug use, transfusion and other medical procedures. In four studies (both peginterferon α-2a,[57;58] two peginterferon α-2b[46;60]) the mode of infection was unknown in 14-22% of participants.

Baseline HCV RNA levels across the seven included studies varied. In the two peginterferon α-2a studies, approximately two thirds of participants had relatively high baseline HCV RNA levels (>500,000 IU/mL[58] or ≥600,000 IU/mL[57]), and one study of peginterferon α-2b[46] also reported high baseline HCV RNA with a mean of 780,000 IU/mL. Two other peginterferon α-2b studies[52;60] reported similar proportions (range 40-55%) of participants with either high (>500,000 or >600,000 IU/mL) or low (<500,000 or <600,000 IU/mL) HCV RNA levels. In the study by Ghaffar and colleagues[47] (peginterferon α-2b) most of the participants had low HCV RNA levels at baseline (median 145,000 IU/mL). The seventh study (peginterferon α-2b[48]) reported a mean HCV RNA of 5 $\log_{10}$ IU/mL, stating that 67% (20/30) of participants had a viral load of $>10^5$ × IU/mL with only one patient having $\log_{10}$ viral load <4.5. Fibrosis levels indicated mild liver disease in most or all of the population across the seven studies, although fibrosis was not reported for all the participants in the study by Ghaffar and colleagues.[47] According to clinical opinion, there is generally no single agreed definition of what constitutes a 'high' or 'low' viral load and the cut-off value is different between the two peginterferons.

Studies differed in the numbers of centres and countries that they included. Four (all peginterferon α-2b) were single-centre studies (Egypt,[47] Kuwait,[46] Poland,[52]and Spain[48]) whilst three (both peginterferon α-2a,[57;58] one peginterferon α-2b[60]) were multi-centre studies (ranging from 6 to 22 centres). Schwarz and colleagues recruited patients from 11 centres all located in the USA[57] whilst the

remaining two studies involved multiple centres in different countries.[58;60] Sokal and colleagues[58] included six centres located in Brazil, the UK (Birmingham Children's Hospital), Belgium, Latvia and Sweden, and Wirth and colleagues[60] included 22 centres located in the USA, South America and Europe. For two studies (one peginterferon α-2a, one peginterferon α-2b), funding was either received from the drug companies involved,[58] or the majority of the authors had received funding from, or were employed by, the drug manufacturer.[60] One study (peginterferon α-2b) did not state the funding source but did report that the drug manufacturer provided the interventions and 'assistance for designing the study'[48] whilst a fourth (peginterferon α-2a) reported unspecified 'additional support' from the drug manufacturer as well as stating other sources.[57] The three remaining peginterferon α-2b studies either received no financial support[46] or reported vaguely that their funding was from 'donations'[47] or 'other departmental sources'.[52]

All seven studies specified the patients' age as an inclusion criterion and this ranged from 3 to 18 years (although the maximum age of included participants was 17 years). All studies required patients to have chronic HCV infection[46-48;52;57;60] and/or detectable plasma HCV RNA,[46-48;52;57;58] although only one study (peginterferon α-2b) specified a detection threshold of HCV RNA for inclusion (>50 IU/mL[48]). Inflammation and/or fibrosis from liver biopsy or ultrasound investigations was specified as supporting evidence of liver disease in four studies (one peginterferon α-2a,[57] three peginterferon α-2b[46;52;60]) and two studies (one peginterferon α-2a,[57] one peginterferon α-2b[47]) explicitly stated that the liver disease should be compensated. Four studies (one peginterferon α-2a, two peginterferon α-2b) specified either that treatment-naïve patients were included[46;58;60] or that patients previously treated with interferon or ribavirin were excluded,[57] whilst one study (peginterferon α-2b) permitted non-responders to interferon-alfa monotherapy provided that they accounted for less than 25% of the population.[48]

Six studies excluded participants who were co-infected with HIV or hepatitis B (not reported in one peginterferon α-2b study[47]) and two studies[47;48] also excluded those who were co-infected with any other non-HCV liver disease Five studies (one peginterferon α-2a, four peginterferon α-2b) excluded those with thrombocytopaenia, anaemia and neutropenia - conditions that are consistent with decompensated liver disease or are made worse by taking peginterferon + ribavirin - by stipulating certain laboratory readings[46;48;57;60] or specifying 'normal levels'[47] in their inclusion/exclusion criteria. Details of other inclusion/exclusion criteria specified by the studies can be found in the data extractions forms in Appendix 4.

Six of the seven studies specified that SVR was the primary outcome.[46;48;52;57;58;60] SVR may also have been the primary outcome in the remaining peginterferon α-2b study (Ghaffar and colleagues[47]), although this was not stated explicitly. In terms of secondary outcomes, EVR was reported by all

seven studies[46-48;52;57;58;60] (though not specifically stated as secondary by Ghaffar and colleagues[47]) and five studies (both peginterferon α-2a,[57;58] three peginterferon α-2b[46;47;52]) reported an end of treatment response (abbreviated to either ETR or EOT). Other secondary virological outcomes reported were RVR,[48;57;60] predictors of viral response,[48;52;57;58;60] virological response at 24 weeks,[48] virological breakthrough,[52] and relapse.[52;57;60] Biochemical response was reported by two peginterferon α-2b studies.[47;60] Adverse events were reported by all seven studies. Four studies (one peginterferon α-2a[58] and three peginterferon α-2b[48;52;60]) reported growth and only one study (peginterferon α-2a) reported QoL.[57]

A summary of the included studies in terms of the patient population, in line with the NICE scope, is given below:

- *Peginterferon α-2a/ α-2b*:
  Peginterferon α-2a, n=2; peginterferon α-2b, n=5
- *Treatment naïve/previously treated*:
  Treatment naïve (100% of population), n=4; mixed treatment (naïve and previously treated), n=2; unclear, n=1
- *Severity of chronic HCV*:
  Mild fibrosis (most or all of the population), n=6; unclear, n=1
- *HIV co-infection*:
  n=0

Table 2 Key characteristics of included studies ordered by date and peginterferon type

Study	Methods	Key inclusion criteria	Key patient characteristics	Outcomes
PEG α-2a + RBV				
Schwarz et al., 2011[57] + related publications[2] [8;50;54-56;62]	*Design*: RCT (but treated as a single cohort study) *Number of centres*: 11 *Country*: USA *Sponsor*: National Institute of Diabetes & Digestive & Kidney Diseases; Food & Drug Administration; National Institutes of Health/National Centre for Research Resources. Additional support from Hoffman-La Roche *Interventions*: PEG IFN α-2a, 180µg/1.73m^2 body surface area/wk (max 180µg) + RBV, 15mg/kg/day (max 1200 mg if ≥75kg and 1,000mg if <75 kg) *Duration:* 48 weeks	Inclusion criteria: • Aged 5-18 years • Chronic HCV infection (plasma HCV RNA on 2 tests ≥ 6 months apart) • Chronic liver disease, as indicated by inflammation and/or fibrosis, consistent with chronic HCV infection on a liver biopsy obtained within the past 36 months; compensated liver disease (Child-Pugh Grade A) • Haemoglobin values >11 g/dL for females; >12 g/dL for males • Normal thyroid stimulating hormone (TSH) • Able to swallow a RBV/placebo tablet	• Mean age: 10.7 years • Male: 27 (49%) • Treatment naïve: 100% • Mean duration of infection: 105 months • Genotype 1: 45 (82%) Genotype 2: 4 (7%) Genotype 3: 6 (11%) Genotype 6: 0 • Vertical transmission 39 (71%); transfusion 6 (11%); other 10 (18%) • Mean HCV RNA: 6.2 $\log_{10}$ IU/mL • HCV RNA ≥600,000 IU/mL: 32 (58%)[a] • Mean ALT: 49 IU//L; >ULN 32 (58%) • Mean AST: 45 IU/L; >ULN 28 (51%) • HAI inflammation: Minimal (1-3): 23 (43%) Mild (4-6): 10 (19%) Moderate (7-9): 19 (35%) Marked (10-12): 2 (4%)	Primary outcome: SVR Secondary outcomes: • RVR • EVR • ETR • Predictors of virological response • Relapse • Adverse events • QoL

	Follow-up: 24 weeks post-treatment *No. participants*: 55 (single arm)	• Signed informed consent from parent/legal guardian Excluded if co-infected with HIV or HBV, or previously treated with IFN or RBV	• Fibrosis score No fibrosis: 7 (13%) Portal-periportal (Ishak 1-2): 43 (80%) Bridging (Ishak 3-4): 4 (7%) Cirrhosis (Ishak 5-6): 0	
Sokal et al., 2010[58]	*Design*: Single cohort study *Number of centres*: 6 *Countries*: Belgium, UK, Sweden, Brazil, Latvia *Sponsor*: Stated funding was from the drug companies involved *Interventions*: PEG IFN α-2a, 100µg/m^2 body surface area/wk (max 180µg) + RBV, 15mg/kg/day (max 1200 mg) *Duration:* 24 or 48 weeks according to genotype	Inclusion criteria: • Treatment-naïve children and adolescents aged 6-17 years • Positive anti-HCV serum antibodies and detectable serum HCV RNA • Not limited by levels of serum aminotransferases, HCV genotype, or mode of infection • All patients presenting with hepatitis C were approached for inclusion • Adequate contraception was compulsory (if applicable) Excluded if co-infected with HIV	• Mean age: not reported for whole group; 11.3 and 12.6 years for subgroups • Male: 30 (46%) • Treatment naïve: 100% • Duration of infection: not reported • Genotype 1: 45 (69%) Genotype 2: 2 (3%) Genotype 3: 16 (25%) Genotype 4: 1 (2%) Genotype 5 or 6: 1 (2%) • Vertical transmission 30 (46%); transfusion 15 (23%); medical procedure 6 (9%); unknown 14 (22%) • HCV RNA <500,000 IU/ml: 23 (36%) >500,000 IU/ml: 42 (65%)	Primary outcome: SVR Secondary outcomes: • EVR • EOT • Predictors of virological response • Safety • Growth

	Follow-up: 24 weeks post-treatment *No. participants*: 65	or HBV	• Fibrosis score No fibrosis: 34 (52%) Grade F1: 21 (32) Grade F2: 9 (14) Also reports key characteristics within genotype subgroups	
PEG α-2b + RBV				
Al Ali et al., 2010[46]	*Design*: Single cohort study *Number of centres*: 1 *Country*: Kuwait Sponsor: none *Interventions*: PEG IFN α-2b, 1.5µg/kg/wk + RBV, 15 mg/kg/day *Duration:* 48 weeks *Follow-up*: 24 weeks post-treatment *No. participants*: 12	Inclusion criteria: • Treatment-naïve patients aged 14-17 years • Detectable HCV RNA • Genotype 4 • Anti-HCV positive liver biopsy findings consistent with the diagnosis of HCV, for whom a decision to treat was made • Patients were included independent of mode of acquisition of infection, level of serum aminotransferases, or serum HCV RNA viral load	• Mean age: 15.75 years • Male: 8 (67%) • Treatment naïve: 100% • Duration of infection: not reported • Genotype 4: 100% • Vertical transmission 2 (17%); IV drug use 2 (17%); transfusion 1 (8%); dental procedures 2 (17%); unknown 5 (42%) • Mean HCV RNA: 0.78 $\times 10^6$ IU/ml (range 0.23-1.8) • Mean serum ALT: 91 IU/L (range 34-194) • Mean METAVIR histological grade: 1.67 (range 1-2) • Mean METAVIR fibrosis score: 0.67	Primary outcome: SVR Secondary outcomes: • EVR • EOT • Adverse events

			(range 0-3)	
Pawlowska et al., 2010[52] + abstract [53]	*Design*: Single cohort study *Number of centres*: 1 *Country*: Poland *Sponsor*: States 'departmental sources' *Interventions*: PEG IFN α-2b, 1.5µg/kg/wk + RBV, 15 mg/kg/day *Duration:* 48 weeks, although also states 24 or 48 weeks according to genotype *Follow-up*: 24 weeks post-treatment *No. participants*: 53	Inclusion criteria: • Children aged 8-17 years • Chronic HCV diagnosed by the presence of serum HCV RNA and histopathological changes in the liver (by liver biopsy & ultrasound) Excluded if co-infected with HIV or HBV	• Mean age: 13.6 years (range 8-17) • Male: 37 (70%) • Treatment naïve 29 (54%); previously treated (IFN α-2b + RBV) 24 (46%) • Mean duration of infection: 5.4 years[b] • Genotype 1: 27 (50%) Genotype 3: 2 (4%) Genotype 4: 24 (46%) • Hospital-acquired transmission 53 (100%), transfusion 5 (9%), surgical procedure 16 (30%)[c] • Mean HCV RNA: 4.56 x10^5IU/mL <500,000 IU/mL: 21 (40%) >500,000 IU/mL: 29 (55%)[d] • Mean serum ALT: 45.8 U/L • Fibrosis score (modified Scheuer scale) ≤ stage 2: 100% • Necroinflammatory score (modified Scheuer scale), ≤ stage 2: 100%	Primary outcome: SVR Secondary outcomes: • EVR • EOT • Relapse • Breakthrough • Non-response • Predictors of virological response • Adverse events • Growth
Wirth et al., 2010[60]	*Design*: Single cohort study	Inclusion criteria: • Children aged 3-17 years with	• Mean age: 10 years • Male: 51 (48%)	Primary outcome: SVR

+ abstract [59]	*Number of centres*: 22 *Countries*: Austria, France, Germany, Italy, Spain, Argentina, Chile, USA, Puerto Rico *Sponsor*: majority of authors received funding or were employed by Schering-Plough *Interventions*: PEG IFN α-2b, 60 μg/m^2 body surface area/wk + RBV, 15 mg/kg/day *Duration*: 24 or 48 weeks according to genotype and viral load *Follow-up*: 24 weeks post-treatment *No. participants*: 107	previously untreated chronic HCV • Evidence of fibrosis and/or inflammatory activity from liver biopsy was requested from all patients before enrollment; however a waiver was permitted for children aged 3-11 years who had an elevated ALT in the year before screening • Absolute neutrophil count ≥ 1500/mm^3; platelet count ≥ 100,000/mm^3; and haemoglobin levels ≥ 11 g/dL for girls and 12 g/dL for boys Excluded if co-infected with HIV or HBV	• Treatment naïve: 100% • Mean duration of infection: 8.5 years • Genotype 1: 72 (67%) Genotype 2: 15 (14%) Genotype 3: 15 (14%) Genotype 4: 5 (5%) • Vertical transmission 75 (70%); parenteral / transfusion 12 (11%); sporadic / not specified 20 (19%) • Mean HCV RNA: 442,748 IU/mL <600,000 IU/ml: 58 (54%) >600,000 IU/ml: 45 (42%) • METAVIR fibrosis score F0: 13 (12.5%); F1: 88 (82.2%); F2: 2 (1.9%); F3: 1 (1%) • Serum ALT normal: 63 (59%); abnormal: 44 (41%) • METAVIR inflammatory activity score none: 6 (6%); mild: 47 (44%); moderate: 32 (30%); severe: 19 (18%); missing: 3 (3%) Also reports key characteristics within age groups	Secondary outcomes: • RVR • EVR • Relapse • Biochemical response • Predictors of virological response • Adverse events • Growth

Ghaffar et al., 2009[47]	*Design*: Single cohort study *Number of centres*: 1 *Country*: Egypt *Sponsor*: stated 'donations' *Interventions*: PEG IFN α-2b, 1.5 µg/kg/wk + RBV, 15mg/kg/d *Duration:* 52 weeks *Follow-up*: 12 months post treatment *No. participants*: 7	Inclusion criteria: • Aged between 8 and 16 years, both genders • Chronic HCV infection (positive antibodies with HCV-RNA positivity and ALT/AST ≤ 1.5 times upper limit of normal) • Well compensated liver disease, normal levels for haemoglobin, platelets, white blood cells, glucose, serum creatinine, normal thyroid profile and negative autoantibodies • No co-infection with any other hepatotrophic virus or HIV	• Age range: 8-13 years • Male: 5 (71%) • Previously treated (IFN): 1 (14%); unclear for other 6 (possibly treatment naïve) • Mean duration of infection: unclear (2 (29%) 4.5 years, 5 (71%) 12.7 years) • Genotype 4a: 1 (14%) Genotype 4b: 5 (71%) Unknown (not tested): 1 (14%) • Vertical transmission 1 (14%); parenteral 5 (71%); both vertical & parenteral 1 (14%) • HCV RNA range: 74,000 – 758,000 IU/mL (median 145,000) • Serum ALT range: 52-223 IU/L (median 77) • Serum AST range: 63-321 IU/L (median 76) • Fibrosis score: not reported for all participants	Primary outcomes: not stated as primary or secondary: • SVR • EVR[e] • ETR • Biochemical response • Side effects (adverse events)
Jara et al., 2008[48]	*Design*: Single cohort study	Inclusion criteria: • Aged between 3 and 16 years	• Mean age: 10 years (range 3.5 – 16) • Male: not reported	Primary outcome: SVR

	Number of centres: 1 *Country*: Spain *Sponsor*: not stated, Schering-Plough provided interventions and assistance for designing the study *Interventions*: PEG IFN α-2b, 1.0µg/kg/wk + RBV, 15mg/kg/d *Duration:* 24 or 48 weeks according to genotype *Follow-up*: at least 24 weeks post-treatment *No. participants*: 30	• Chronic HCV, defined serum HCV RNA titres (>50 IU/ml) for ≥ 3 years with continuous or intermittently elevated ALT values • Non-responders to IFN-α monotherapy eligible if they accounted for < 25% of the patient population Excluded if co-infected with HIV or non-HCV liver disease	• Treatment naïve: 24 (80%); previously treated (IFN α monotherapy) 6 (20%) • Duration of infection: not reported • Genotype 1: 26 (87%) Genotype 3: 3 (10%) Genotype 4: 1 (3%) • Vertical transmission 21 (70%), parenteral 9 (30%) • Mean HCV RNA: 5 $\log_{10}$IU/ml (range 3-6)[f] • Mean serum ALT: 75 IU/L (range 29-232) • Mean serum AST: 52 IU/L (range 24-157) • Knodell fibrosis score <4: 58%; 4-7: 31%; ≥ 8: 10%	Secondary outcomes: • RVR[e] • EVR[e] • Virological response[e] • Predictors of SVR • Biochemical response • Safety (adverse events) • QoL • Growth

ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOT/ETR, end of treatment virological response; EVR, early virological response; HAI, histological activity index; HCV RNA, hepatitis C virus ribonucleic acid; PEG-IFN α, pegylated interferon alfa; RBV, ribavirin; SVR, sustained virological response; ULN, upper limit of normal; QoL, quality of life.
[a]reported as 32 (70%) in publication;
[b]abstract states 8.5 years;
[c]more than one mode of HCV infection;
[d]three patients not accounted for;
[e]not defined by study authors but classified by reviewer according to data reported at specific time points;
[f]reports a viral load of $>10^5$ x IU/mL in 67% (20/30), with only one patient having $\log_{10}$ viral load <4.5.

Quality assessment of included studies

The methodological quality of reporting in the included studies was assessed using criteria based on guidance by the Centre for Reviews and Dissemination (CRD) at the University of York,[43] and is shown in Table 3. The quality assessment criteria relate to various aspects of study design which may help to gauge the relative strengths and weaknesses of the individual studies. On the whole, the cohort studies were of generally poor quality, although the study by Schwarz and colleagues[57] (peginterferon α-2a) fared better in its reporting of methodological details. This was an RCT, although as detailed previously, is treated as a single cohort study in this assessment.

All the studies specified their criteria for patient selection *a priori*, stating their inclusion and exclusion criteria to varying degrees of detail (although Ghaffar and colleagues[47] did not specify any exclusion criteria). The lack of randomisation procedures (due to the single arm study design of most studies) may mean there is a higher risk of bias. Given that six of the seven studies were uncontrolled cohort studies with only one intervention arm, the lack of blinding of participants was not applicable. The seventh study by Schwarz and colleagues[57] reported that participants (in both arms) and investigators were blinded as to whether they were receiving placebo or ribavirin in combination with peginterferon α-2a, with placebo/ribavirin tablets being supplied in the same dosing regimen.

For most of the studies it was unclear whether the authors measured more outcomes than they reported. Schwarz and colleagues[57] (peginterferon α-2a) was the only study to clearly specify measuring more outcomes than were reported (either in the main paper[57] or related publications[28;49-51;54-56]), stating that assessments of body composition and growth would be reported separately. (A recent publication[63] reporting these outcomes did not meet the inclusion criteria for the review as combined results were reported for the peginterferon α-2a combination and monotherapy groups together). Pawlowska and colleagues[52] reported that there were plans to assess growth 5 years after treatment cessation but there were no further details. Most of the studies provided adequate details of participant withdrawals and losses to follow-up, with the exception of two peginterferon α-2b studies[47;52] where this information was not reported. However, four studies (one peginterferon α-2a,[58] three peginterferon α-2b[46;47;60]) reported very little or no methodology relating to data analysis and all seven studies were either not clear, or did not report, whether the statistical analysis accounted for any missing data.

Assessment of the generalisability of the studies is difficult owing to the single cohort study design, poor methodological quality, variation in their participant inclusion criteria and countries included, as well as other uncertainties.

Table 3 Assessment of study quality

Quality criteria	Schwarz 2011[57]	Sokal 2010[58]	Wirth 2010[60]	Pawlowska 2010[52]	Al Ali 2010[46]	Ghaffar 2009[47]	Jara 2007[48]
Selection criteria predefined	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blinding of participants	Yes	n/a	n/a	n/a	n/a	n/a	n/a
More outcomes measured than reported	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Withdrawals and drop-outs described	Yes[a]	Yes	Yes	NR	Yes	NR	Yes
Analysis - accounts for missing data	Unclear	Unclear	Unclear	No	Unclear	n/a[b]	No
- if so, were methods appropriate	n/a	n/a	n/a	n/a	n/a	n/a	n/a

n/a, not applicable; NR, not reported.
[a]Numbers, timing and reasons for dropouts reported but unclear whether 4 patients who discontinued the drug were classified as dropouts.
[b]no analysis conducted.

4.2 Assessment of effectiveness

The included studies of peginterferon alfa in the following section provide no evidence of a comparative nature, either versus BSC or against each other. It should be noted that these single cohort studies reported few or no statistical analyses on the data. Therefore the narratives reported in this section are based on observation of the data and should be interpreted with caution.

4.2.1 Sustained virological response

SVR was reported to be the primary outcome in six of the included studies, but not specifically stated as such in the seventh (Ghaffar and colleagues[47]). Results are reported in Table 4.

SVR was defined as undetectable serum HCV RNA 24 weeks after the end of treatment in six studies (both peginterferon α-2a studies[57;58] and four peginterferon α-2b studies[46;48;52;60]) and 12 months after

the end of treatment in one study (Ghaffar and colleagues[47]). Three studies specifically defined the lower limit of detection for attainment of SVR to be 50 IU/mL,[58] <50 IU/mL[46] or <10 IU/mL[57] (although the latter is reported to be <100 IU/mL in two related publications[55;56]). Quantitative and qualitative lower limits of detection of HCV RNA are reported by most of the other studies,[48;52;60] ranging from 25 to 600 IU/mL, but it is not always clear which virological outcome they relate to (i.e. EVR, EOT, SVR). Details for individual studies can be seen in the data extraction forms in Appendix 4.

Peginterferon α-2a

SVR rates were similar in the two studies evaluating peginterferon α-2a,[57;58] ranging from 53-66%. The longer-term follow-up of participants in the PEDS-C trial[57] found that for those children who achieved an SVR who were followed up for 2 years (45/55 (82%)), durability of viral response was 100%.

Peginterferon α-2b

For those receiving peginterferon α-2b, SVR rates across five studies[46-48;52;60] ranged from 29% to 75%. The two studies[46;47] reporting the lowest and highest rates in this range had very small participant numbers which may raise a question over the reliability of the data, and both were in all, or mostly, genotype 4 children. Excluding these two very small studies,[46;47] the SVR rates in those receiving peginterferon α-2a appear comparable to those receiving peginterferon α-2b (range 49-65%).

It should be noted that the study by Jara and colleagues[48] used a lower dose of peginterferon α-2b compared to the other studies (1.0µg/kg/week versus 1.5µg/kg/week) but it is unclear whether this had an impact on the rate of SVR achieved.

Table 4 Sustained virological response

Study	**Treatment: PEG α-2a**	**SVR % (n/N)**
Schwarz, 2011[57]	PEG α-2a + RBV 48 weeks, n=55	53%, 95% CI 40-66% (29/55)
Sokal, 2010[58]	PEG α-2a + RBV 24 or 48 weeks, n=65	66% (43/65)[a] (2 ND)
Study	**Treatment: PEG α-2b**	**SVR % (n/N)**
Al Ali, 2010[46]	PEG α-2b + RBV 48 weeks, n=12	75% (9/12)
Pawlowska, 2010[52]	PEG α-2b + RBV 24 or 48 weeks, n=53	49% (26/53)[b]

Wirth, 2010[60]	PEG α-2b + RBV 24 or 48 weeks, n=107	65% (70/107)
Ghaffar, 2009[47]	PEG α-2b + RBV 52 weeks, n=7	29% (2/7)
Jara, 2007[48]	PEG α-2b + RBV 24 or 48 weeks, n=30	50% (15/30)

ND, not defined by authors but assumed to be 'not determined'; PEG α, peginterferon alfa; RBV, ribavirin; SVR, sustained virological response.
[a]Data were reported for genotype subgroups from which the overall population data were calculated by the reviewer.
[b]Abstract reports an SVR of 47% for whole group.[53]

4.2.2 SVR according to prognostic factors

It should be noted that there were some differences between studies in the SVR subgroups in terms of how different categories were defined (e.g. low/high viral load, abnormal ALT) and also inconsistencies in grouping different categories (e.g. genotypes, histology). These differences should be borne in mind when interpreting the results. Furthermore, numbers in some of the SVR subgroups were very small and are unlikely to be statistically powered, so results should be interpreted with caution.

Genotype

Sustained virological response rates according to HCV genotype were reported by both of the peginterferon α-2a studies[57;58] and three peginterferon α-2b studies[48;52;60] and are shown in Table 5.

Peginterferon α-2a

The PEDS-C study by Schwarz and colleagues[57] grouped HCV genotypes into 'genotype 1' and 'genotype 2-6' which is slightly unusual as genotypes are generally grouped according to response to treatment, whereby genotypes 2 and 3 would be grouped together and genotypes 1, 4, 5 and 6 would be grouped together. However, in the peginterferon α-2a and ribavirin treatment arm of the PEDS-C trial (the only arm of PEDS-C considered in this review), there were no participants with genotypes 4, 5 or 6 so the 'genotype 2-6' group actually only consists of children with genotypes 2 and 3. Additionally, in the other peginterferon α-2a study by Sokal and colleagues,[46] there were only 2/65 (3%) participants with genotypes 4, 5 or 6 so the grouping of 'genotype 1, 4, 5 or 6' contained predominantly genotype 1 participants (and hence this group has been considered genotype 1 in the following section).

Response rates within each genotype group were similar across the two studies evaluating peginterferon α-2a.[57;58] SVRs for participants with genotype 1 ranged from 47-57%, whilst response

rates for genotype 2 or 3 were observed to be higher, ranging from 80-89%. Sokal and colleagues[58] reported that the SVR rates were statistically significantly higher for those with genotype 2 or 3 compared to genotype 1, 4, 5 or 6 (89% versus 57%, p<0.01).

Peginterferon α-2b

SVRs for genotype 1 were similar across the three peginterferon α-2b studies, ranging from 46-53%.[48;52;60] Response rates for genotype 2 or 3 were observed to be more variable and higher, with an overall range of 50-100%. However, one study grouped both genotype 2 and 3 together,[60] whilst two studies[48;52] reported only on genotype 3 and the numbers of participants with genotype 3 in these two studies were very small (1 of 2[52] and 3 of 3[48]). SVRs for genotype 4 in the three peginterferon α-2b studies[48;52;60] varied greatly, ranging from 0-80%; the numbers of participants as a proportion of the total study population in these genotype 4 subgroups were very small in two of these studies (1 of 30[48] and 5 of 107[60]) which may explain some of the variation.

Pawlowska and colleagues[52] examined differences in SVR rates but found no statistically significant difference in SVR between those with HCV genotype 1 and 4 (48% versus 50% respectively), although no quantitative statistics or p-values were reported.

Table 5 SVR according to genotype

Study	**Treatment: PEG α-2a**	**SVR according to genotype**	
		Genotype	**SVR % (n/N)**
Schwarz, 2011[57]	PEG α-2a + RBV 48 weeks, n=55	Genotype 1 Genotype 2-6[a]	47%, 95% CI 32-61% (21/45) 80%, 95% CI 55-100% (8/10)
Sokal, 2010[58]	PEG α-2a + RBV 24 or 48 weeks, n=65	Genotype 1, 4, 5 or 6[b] Genotype 2 or 3	57% (27/47) (1 ND) 89% (16/18) (1 ND)
Study	**Treatment: PEG α-2b**	**SVR according to genotype**	
		Genotype	**SVR % (n/N)**
Pawlowska, 2010[52]	PEG α-2b + RBV 24 or 48 weeks, n=53	Genotype 1 Genotype 3 Genotype 4	48% (13/27) 50% (1/2) 50% (12/24)
Wirth, 2010[60]	PEG α-2b + RBV 24 or 48 weeks, n=107	Genotype 1 Genotype 2 or 3 Genotype 4	53% (38/72) 93% (28/30) 80% (4/5)
Jara, 2007[48]	PEG α-2b + RBV	Genotype 1	46% (12/26)

	24 or 48 weeks, n=30	Genotype 3	100% (3/3)
		Genotype 4	0 (0/1)

ND, not defined by authors but assumed to be 'not determined'; PEG α, peginterferon alfa; RBV, ribavirin; SVR, sustained virological response.
[a]No participants with genotypes 4, 5 or 6, thus all are genotype 2 or 3.
[b]n=2 participants with genotypes 4, 5 or 6 and n=45 with genotype 1.

Viral load

Three studies (both the peginterferon α-2a studies[57;58] and one peginterferon α-2b study[60]) reported SVR according to baseline viral load, stratified into low (<500,000 or ≤600,000 IU/mL) or high (>500,000 or ≥600,000 IU/mL) HCV RNA viral load (Table 6).

Peginterferon α-2a

By observation of values in the two studies, children with low baseline viral load appear to have achieved higher SVRs (range 70-74%) compared to those with a higher viral load at baseline (range 50-55%). Sokal and colleagues[58] also reported SVRs according to both baseline viral load and genotype. The results appear to show that a greater proportion of children with genotype 2 or 3 achieved an SVR compared to those with genotype 1, 4, 5 or 6 regardless of viral load.

Peginterferon α-2b

The peginterferon α-2b study (Wirth and colleagues[60]) also found that children with low baseline viral load were more likely to achieve an SVR compared to those with a higher viral load at baseline (79% versus 49% respectively) based on observation of the data. When groups were further split by genotype, SVR rates were higher in children with genotype 2 or 3 (100%) compared to genotype 1 or 4 (0-29%) in those with high viral load. For those with low baseline viraemia, SVRs were higher in children with genotype 2 or 3 (94%) than genotype 1 (72%), but lower than genotype 4 (100%). Wirth and colleagues[60]reported that in genotype 1 patients, the SVR was statistically significantly higher in those with low baseline viral load compared to those with high baseline viral load (72% versus 29% respectively, p=0.0006).

Table 6 SVR according to baseline viral load

Study	**Treatment: PEG α-2a**	**SVR according to viral load**	
		HCV RNA	**SVR % (n/N)**
Schwarz, 2011[57]	PEG α-2a + RBV	<600,000 IU/mL	70% (16/23)
	48 weeks, n=55	≥600,000 IU/mL	50% (16/32)
Sokal, 2010[58]	PEG α-2a + RBV	<500,000 IU/mL	74% (17/23)
	24 or 48 weeks, n=65	Genotype 2 or3	90% (9/10)
		Genotype 1, 4, 5 or 6	62% (8/13)

		>500,000 IU/mL	55% (22/40)
		Genotype 2 or 3	100% (7/7)
		Genotype 1, 4, 5 or 6	45% (15/33)
Study	**Treatment: PEG α-2b**	**SVR according to viral load**	
		HCV RNA	**SVR % (n/N)[a]**
Wirth, 2010[60]	PEG α-2b + RBV	≤600,000 IU/mL	79% (46/58)[b]
	24 or 48 weeks, n=107	Genotype 1	72% (28/39)[c]
		Genotype 2 or 3	94% (15/16)
		Genotype 4	100% (3/3)
		>600,000 IU/mL	49% (22/45)[b]
		Genotype 1	29% (9/31)[c]
		Genotype 2 or 3	100% (13/13)
		Genotype 4	0 (0/1)

HCV RNA, hepatitis C virus ribonucleic acid; PEG α, peginterferon alfa; RBV, ribavirin; SVR, sustained virological response.
[a]reports missing data: 1/2 genotype 1, 0/1 genotype 2/3, 1/1 genotype 4 but baseline viral load of those with missing data not known.
[b]totals calculated by reviewer.
[c]p=0.0006 for low versus high viral load in genotype 1 cohort.

Previous treatment history

Peginterferon α-2a

Both of the peginterferon α-2a studies[57;58] evaluated only treatment naïve children and SVR results are reported in Table 4 and discussed previously.

Peginterferon α-2b

Two peginterferon α-2b studies[48;52] that recruited both treatment naïve and previously treated participants reported SVR rates separately by treatment history (Table 7). In the study by Pawlowska and colleagues,[52] approximately half of the children had been previously treated with non-pegylated interferon α-2b plus ribavirin for 12 months, 2-5 years earlier, whilst one fifth of the children in the study by Jara and colleagues[48] had received treatment with non-pegylated interferon monotherapy 3-5 years earlier.

As can be seen in Table 7, higher rates of SVR were achieved in participants who were treatment naïve (55-62%) compared to those who had been previously treated (17-33%). Pawlowska and colleagues[52] also reported SVR rates further split by genotype group. Higher SVR rates were again observed in those who were treatment naïve compared to previously treated participants for both genotypes 1 and 4 (both genotype 3 participants were treatment naïve). It should be noted that numerators in the genotype subgroups do not add up correctly to the total number of treatment naïve

and previously treated participants, and also that participant numbers in these subgroups were small and hence these results should be viewed with caution.

Table 7 SVR according to previous treatment history

Study	Treatment: PEG α-2b	SVR according to previous treatment	
		Treatment history	**SVR % (n/N)**
Pawlowska, 2010[52]	PEG α-2b + RBV 24 or 48 weeks, n=53	Treatment naïve	62% (18/29)[a]
		Genotype 1	62% (10/16)
		Genotype 3	50% (1/2)
		Genotype 4	72% (8/11)
		Previously treated	33% (8/24)[a]
		Genotype 1	27% (3/11)
		Genotype 3	n/a[b]
		Genotype 4	30% (4/13)
Jara, 2007[48]	PEG α-2b + RBV 24 or 48 weeks, n=30	Treatment naïve	55% (11/20)[c]
		Previously treated	17% (1/6)[c]

PEG α, peginterferon alfa; RBV, ribavirin; SVR, sustained virological response.
[a]Numerators in the genotype subgroups (as reported in the publication) do not add up correctly to the total number of treatment naïve and previously treated participants.
[b]No previously treated patients had genotype 3.
[c]Of 30 patients, only 26 were included, all genotype 1; remaining 4 patients (3 x genotype 3, 1 x genotype 4, all treatment naïve) were not included.

Baseline ALT levels

Three included studies reported SVR according to ALT levels at baseline, although none defined 'normal' or 'abnormal' levels *per se*. Results are shown in Table 8. As mentioned below (section 4.2.5), there appears to be no clear consensus on what would be considered 'normal' ranges of ALT concentrations in children and young adults.

Peginterferon α-2a

Both of the peginterferon α-2a studies[57;58] reported SVR according to baseline ALT levels. For both studies, the rate of SVR was higher in those with normal ALT levels at baseline (range 70-80%) compared to those whose baseline ALT levels were not normal (range 41-58%) (described as either abnormal[58] or ALT> upper limit of normal[57]). Sokal and colleagues[58] also reported results further split by genotype. For children with normal ALT at baseline, SVR was not affected by genotype. However, for children with abnormal ALT at baseline, those with the more favourable genotype 2 or 3 appeared to have a higher SVR rate than those with genotype 1, 4, 5 or 6 (largely genotype 1 as previously stated). Sokal and colleagues[58] also reported that in children with genotype 1, 4, 5 or 6, the

SVR was statistically significantly higher in those with normal baseline ALT compared to those with abnormal baseline ALT (89% versus 37% [although the text in the publication states 36%], $p<0.001$).

Peginterferon α-2b

Wirth and colleagues[60] was the only peginterferon α-2b study that reported SVR by baseline ALT levels (Table 8). Unlike the two peginterferon α-2a studies, SVR appeared to be similar regardless of whether participants had normal or abnormal levels of ALT at baseline (67% and 64% respectively). Results were further split by genotype. For children with normal ALT at baseline, those with the more favourable genotype 2 or 3 appeared to have a higher SVR rate than those with genotype 1 or 4. This was also the case for children with abnormal baseline ALT where those with genotype 2 or 3 had higher SVR rates compared to genotype 1, but not genotype 4. However, there were only three children in the latter subgroup so these results should be interpreted with caution.

Table 8 SVR according to baseline ALT

Study	**Treatment: PEG α-2a**	**SVR according to ALT levels**	
		ALT	**SVR % (n/N)**
Schwarz, 2011[57]	PEG α-2a + RBV 48 weeks, n=55	Normal ALT ALT > ULN	70%, 95% CI 51-88% (16/23) 41%, 95% CI 24-58% (13/32)
Sokal, 2010[58]	PEG α-2a + RBV 24 or 48 weeks, n=65	Normal ALT Genotype 2 or 3 Genotype 1, 4, 5 or 6 Abnormal ALT[a] Genotype 2 or 3 Genotype 1, 4, 5 or 6	80% (24/30) 89% (8/9) 89% (17/19) 58% (19/33) 100% (8/8) 37%[b] (10/27)
Study	**Treatment: PEG α-2b**	**SVR according to ALT levels**	
		ALT	**SVR % (n/N)**
Wirth, 2010[60]	PEG α-2b + RBV 24 or 48 weeks, n=107	Normal ALT Genotype 1 Genotype 2 or 3 Genotype 4 Abnormal ALT[a] Genotype 1 Genotype 2 or 3 Genotype 4	67% (42/63)[c] 56% (23/41) 90% (18/20) 50% (1/2) 64% (28/44)[c] 48% (15/31) 100% (10/10) 100% (3/3)

ALT, alanine aminotransferase; PEG α, peginterferon alfa; RBV, ribavirin; SVR, sustained virological response; ULN, upper limit of normal.
[a]not defined.
[b]data are from a table in the publication; also states 36% in the publication text.
[c]calculated by reviewer.

Liver histology

Peginterferon α-2a

Both the peginterferon α-2a studies[57;58] reported SVR according to baseline liver histology (Table 9). Schwarz and colleagues[57] reported SVRs according to fibrosis stage (none or stage 1-6) using the Ishak fibrosis classification system, as well as inflammation (minimal, grade 1-3 or mild-marked, grade 4-12) using the Knodell histological activity index (HAI). Both are commonly used systems for classifying liver biopsy samples and determine the severity of HCV infection. A more detailed explanation of biopsy classification systems, and their comparability, is available in section 1.1. Sokal and colleagues[58] reported SVRs according to fibrosis or no fibrosis but did not specify which fibrosis classification system was used, making direct comparisons difficult. Those with fibrosis were classified into F1 and F2 only, indicating mild liver disease.

There did not appear to be any impact of the degree of liver fibrosis on SVR rates. For children with no liver fibrosis at baseline, SVRs were 43% in one study[57] compared to 76% in the second study,[58] although it should be noted that there were only seven participants in this subgroup in the PEDS-C study.[57] In children with some degree of fibrosis, rates of SVR were more similar between the two studies (53%[57] and 60%[58]). Sokal and colleagues[58] further stratified SVRs by genotype with SVR rates observed to be higher in those with genotype 2 or 3 compared to genotype 1, 4, 5 or 6 regardless of the level of baseline fibrosis.

In the PEDS-C study by Schwarz and colleagues,[57] rates of SVR appeared lower in children with a lower grade of disease activity compared to those with mild-marked liver inflammation (43% versus 58% respectively), although it should be noted that confidence intervals for both groups were wide.

Peginterferon α-2b

No peginterferon α-2b studies reported SVR according to liver histology.

Table 9 SVR according to baseline liver histology

Study	Treatment: PEG α-2a	SVR according to liver histology	
		Histological parameter	**SVR % (n/N)**
Schwarz, 2011[57]	PEG α-2a + RBV 48 weeks, n=55	Fibrosis stage None	 43%, 95% CI 6-80%

			(3/7)
		Stage 1-6	53%, 95% CI 39-67% (25/47)
		Inflammation HAI	
		Minimal (1-3)	43%, 95% CI 23-64% (10/23)
		Mild-Marked (4-12)	58%, 95% CI 41-75% (18/31)
Sokal, 2010[58]	PEG α-2a + RBV 24 or 48 weeks, n=65	No fibrosis	76% (25/33)
		Genotype 2,3	100% (8/8)
		Genotype 1,4,5,6	68% (17/25)
		Fibrosis	60% (18/30)
		Genotype 2,3	89% (8/9)
		Genotype 1,4,5,6	48% (10/21)

HAI, histological activity index; PEG α, peginterferon alfa; RBV, ribavirin; SVR, sustained virological response.

Multivariate analysis of predictors of SVR

Only one study, PEDS-C,[57] used a multivariate approach to explore factors predictive of SVR (based on a logistic model). However, the PEDS-C trial included data from a placebo monotherapy arm which is outside the scope of the current assessment. The following significant predictors of SVR were identified (for full results see the data extraction form - Appendix 4): female sex; non-maternal HCV transmission; genotype non-1; moderate or marked liver inflammation; absence of steatosis; and lower baseline levels of HCV RNA.

4.2.3 Virological response during treatment

All seven included studies reported virological response at various time points during treatment, including rapid virological response (RVR), early virological response (EVR) and end of treatment response (abbreviated to either EOT or ETR in the publications; the former is used hereafter for consistency). RVR is defined as a viral load that does not exceed a specified (although not standardised) limit after 4 weeks of therapy. EVR can be defined as complete EVR, which means HCV RNA is undetectable after 12 weeks, or partial EVR which means virus is still detectable but there has been at least a 2 $\log_{10}$ drop compared to the baseline value.

RVR was reported by two studies (one peginterferon α-2a[57] and one peginterferon α-2b[48]) although in the PEDS-C study[57] it was defined as a lack of detectable HCV RNA at week 5 of treatment (rather than at week 4). Jara and colleagues[48] reported the proportion of children with negative HCV RNA at

week 4 of treatment, which we infer to be RVR, although this was not explicitly defined as such by the authors. All seven studies reported EVR. Three peginterferon α-2b studies did not specifically define EVR but reported undetectable[47;60] or negative[48] HCV RNA at week 12 of treatment, which we infer to be EVR. A fourth peginterferon α-2b study[46] defined EVR as an HCV RNA level <50 IU/mL at week 12 compared to baseline, whilst the two peginterferon α-2a studies defined EVR as a decrease of $\geq$ 2 logs at week 12 compared to baseline.[57;58] Pawlowska and colleagues[52] described EVR as 'levels of HCV RNA viral load at week 12 of treatment' but did not specify if levels had to be undetectable or reach a lower limit (but did define these for the sub-categories of complete and partial EVR – see data extraction form in Appendix 4). Six of the included studies reported EOT, defined as undetectable HCV RNA at the end of treatment (48 weeks,[52;57] 52 weeks,[47] 24 or 48 weeks[58]) or HCV RNA <50 IU/mL at week 48.[46] The sixth study (Wirth and colleagues[60]) reported EOT but did not provide a definition. Results can be seen in Table 10.

Peginterferon α-2a

Only one peginterferon α-2a study (Schwarz and colleagues[57]) presented results for RVR. The proportion of participants who achieved an RVR (at week 5) was 24%. Both studies reported similar rates of EVR, ranging from 59-65%. Sokal and colleagues[58] performed a statistical comparison between the genotype subgroups and found that children with genotype 2 or 3 achieved a significantly higher EVR than those with genotype 1, 4, 5 or 6 (83% versus 57% respectively, $p<0.05$). EOT rates were also similar between the two peginterferon α-2a studies (64% at 48 weeks[57] and 68% at 24 or 48 weeks[58]). Sokal and colleagues[58] again reported a statistically significant difference between the genotype subgroups whereby 94% of children with genotype 2 or 3 achieved an EOT compared to 57% of children with genotype 1, 4, 5 or 6 ($p<0.001$).

Peginterferon α-2b

One peginterferon α-2b study (Jara and colleagues[48]) reported RVR with only one participant (3%) achieving an RVR at week 4 which is lower than that reported in the peginterferon α-2a study.[57] EVR ranged from 52% to 83% across four peginterferon α-2b studies,[46;48;52;60] whilst the very small study by Ghaffar and colleagues[47] was an outlier reporting a much lower rate (29%). EOT rates were similar across three of the four peginterferon α-2b studies that reported them,[46;52;60] with a range of 66% to 83%, whilst again Ghaffar and colleagues' study[47] was an outlier, reporting a lower EOT response rate (43% at week 52) compared to the other studies (66%[52] and 83%[46] at week 48, and 70% at week 24 or 48[60]).

Table 10 Virological response during treatment

Study	Treatment: PEG α-2a	Virological response	
		Virological parameter	**% with response (n/N)**
Schwarz, 2011[57]	PEG α-2a + RBV 48 weeks, n=55	RVR (week 5) EVR (week 12) EOT (week 48)	24% (13/55)[a] 59% (32/55)[a] 64%[b] (35/55)[a]
Sokal, 2010[58]	PEG α-2a + RBV 24 or 48 weeks, n=65	EVR (week 12) EOT (week 24 or 48)	65% (42/65)[c] (3ND) 68% (44/65)[c] (2 ND)
Study	**Treatment: PEG α-2b**	**Virological response**	
		Virological parameter	**% with response (n/N)**
Al Ali, 2010[46]	PEG α-2b + RBV 48 weeks, n=12	EVR (week 12) EOT (week 48)	83% (10/12) 83% (10/12)
Pawlowska, 2010[52]	PEG α-2b + RBV 24 or 48 weeks, n=53	EVR (week 12) EOT (week 48)	77% (41/53) 66% (35/53)
Wirth, 2010[60]	PEG α-2b + RBV 24 or 48 weeks, n=107	EVR (week 12) EOT (week 24 or 48)	68% (73/107)[d] 70% (75/107)[d]
Ghaffar, 2009[47]	PEG α-2b + RBV 52 weeks, n=7	EVR (week 12)[e] EOT (week 52)	29% (2/7) 43% (3/7)
Jara, 2007[48]	PEG α-2b + RBV 24 or 48 weeks, n=30	RVR (week 4)[e] EVR (week 12)[e]	3% (1/30) 52% (15/29)

EOT, end of treatment virological response; EVR, early virological response; ND, not defined by authors but assumed to be 'not determined'; PEG α, peginterferon alfa; RBV, ribavirin; RVR, rapid virological response; VR, virological response.
[a]n calculated by reviewer.
[b]reports 65% in text.
[c]overall population data calculated by reviewer as data reported for genotype subgroups only. Response rates reported inconsistently in the text and tables of the publication; the data extracted above are based on all patients in each group – see data extraction form in Appendix 4for further details.
[d]overall population data calculated by reviewer as data reported for subgroups only.
[e]not defined by study authors but classified by reviewer according to data reported at specific time points.

4.2.4 Non-response and relapse

Five studies (both the peginterferon α-2a studies[57;58] and three peginterferon α-2b studies[46;48;52]) reported the proportion of participants who did not respond to treatment, although a specific definition of non-response was not given by any of the studies. Five studies (one peginterferon α-2a study[57] and four peginterferon α-2b studies[46;48;52;60]) reported data for participants who relapsed. Relapse was defined by three studies as the re-appearance of HCV RNA (detectable HCV RNA at week 72,[52] at last follow-up[60] or after stopping therapy[57]) after previously having undetectable HCV RNA at the end of treatment. Two of the peginterferon α-2b studies reported data but did not specifically define relapse.[46;48] Results can be seen in Table 11.

Peginterferon α-2a

Both peginterferon α-2a studies presented results for non-response,[57;58] and this ranged from 12-25%. The proportion of participants with virological relapse was only reported in the PEDS-C study[57] and was found to be 17%.

Peginterferon α-2b

Rates of non-response in the three peginterferon α-2b studies[46;48;52] varied, with one study (Al Ali and colleagues[46]) reporting a rate of 17% which was similar to those reported in the two peginterferon α-2a studies. The authors[46] stated that the two non-responders had baseline HCV RNA levels that were higher than that of most of the other patients, but do not provide any quantitative data to support this. The other two studies[48;52] reported higher rates, ranging from 47-51%.

The proportion of participants with virological relapse reported in four peginterferon α-2b studies[46;48;52;60] ranged from 3-17%. Wirth and colleagues[60] stated that relapse only occurred in patients with genotype 1.

Table 11 Non-response and relapse

Study	**Treatment: PEG α-2a**	**Non-response % (n/N)**	**Relapse % (n/N)**
Schwarz, 2011[57] + related publication[28]	PEG α-2a + RBV 48 weeks, n=55	25% (14/55)	17% (9/55)[a]
Sokal, 2010[58]	PEG α-2a + RBV 24 or 48 weeks, n=65	12% (8/65)[b]	NR
Study	**Treatment: PEG α-2b**	**Non-response % (n/N)**	**Relapse % (n/N)**
Al Ali, 2010[46]	PEG α-2b + RBV 48 weeks, n=12	17% (2/12)	8% (1/12)
Pawlowska, 2010[52] + abstract[53]	PEG α-2b + RBV 24 or 48 weeks, n=53	51% (27/53)	17% (9/53)[c]
Wirth, 2010[60]	PEG α-2b + RBV 24 or 48 weeks, n=107	NR	12% (9/72)[d] 8% (9/107)[e]
Jara, 2007[48]	PEG α-2b + RBV 24 or 48 weeks, n=30	47% (14/30)	3% (1/30)

NR, not reported; PEG α, peginterferon alfa; RBV, ribavirin.
[a]n calculated by reviewer.
[b]all patients with non-response had genotypes 1, 4, 5 or 6 (none had genotypes 2/3)
[c]abstract reports a relapse rate of 7.5% for whole group but assumed to be an error.
[d]n calculated by reviewer; all patients who relapsed had genotype 1.
[e]calculated by reviewer for whole cohort.

4.2.5 Biochemical response

Peginterferon α-2a

Neither of the two studies on peginterferon α-2a reported biochemical outcomes.

Peginterferon α-2b

Three of the five studies on peginterferon α-2b reported changes in liver enzyme concentrations in response to treatment. In the small study by Ghaffar and colleagues,[47] median concentrations of serum ALT and AST had each declined to around 50% of their baseline values after 52 weeks (the statistical significance of these changes was not reported) (Table 12). Two larger studies[48;60] mentioned changes in ALT but did not report absolute values of ALT concentrations. Wirth and colleagues[60] reported that normalisation of ALT occurred in 34 of 44 patients (77%) who had elevated ALT at baseline. Jara and colleagues[48] mentioned that 28 of 30 patients (93%) had elevated ALT levels at baseline; in 14 of 15 children (93%) who attained an SVR during the first month, ALT values normalised and remained normal throughout the treatment and follow up.

The ranges of ALT and AST concentrations found in these studies are difficult to compare to what would be considered 'normal' ranges in clinical practice, since (based on clinical expert opinion) there are no universally agreed standard reference ranges for children, and the concentrations that would be considered 'normal' vary between laboratories and age groups.

Table 12 Biochemical response

Study	Treatment: PEG α-2b	Biochemical response [a]	
		Baseline, median (range)	Post-treatment week 52, median (range)
Ghaffar, 2009[47]	PEG α-2b + RBV 52 weeks, n=7	ALT: 77 (52-223) IU/L AST: 76 (63-321) IU/L	ALT: 39 (17-63) IU/L AST: 38 (20-69) IU/L

ALT, alanine aminotransferase; AST, aspartate aminotransferase; PEG α, peginterferon alfa; RBV, ribavirin.
[a]statistical significance of differences between baseline and week 52 assessments not reported.

4.2.6 Histological response

Peginterferon α-2a

Neither of the two studies on peginterferon α-2a reported histological outcomes.

Peginterferon α-2b

Only the small study by Ghaffar and colleagues[47] reported changes in histology in response to treatment. However, results were only provided for four of the seven participants. Based on the HAI,

three patients showed a small improvement relative to baseline and one patient exhibited fibrosis regression. As these results were based on a subgroup of a very small population, they should be interpreted with caution.

4.2.7 Quality of life

Peginterferon α-2a

Only the PEDS-C study[57] reported changes in participants' QoL, assessed using the Child Health Questionnaire (CHQ) – Parent Form 50.[27;28;54] PEDS-C also reported changes in participants' behavioural and emotional functioning (using the Child Behaviour Checklist - CBCL), depression (using the Children's Depression Inventory - CDI), and cognitive functioning (using the Behaviour Rating Inventory of Executive Function – BRIEF) which may assist interpretation of QoL.[28;54] The CHQ, CBCL and BRIEF instruments were all completed by the child's parent or guardian whilst the CDI was completed by the child.

The CHQ yielded two composite scores for physical health and psychosocial functioning, as well as scores for 11 different scales (physical functioning; role/social limitations (emotional, physical); general health; bodily pain/discomfort; parent impact (emotional, time); self-esteem; mental health; general behaviour; and family impact). Scores ranged from 0-100, with higher scores reflecting better QoL. The CBCL yielded three composite scores for internalising, externalising and total behaviour problems, and eight clinical scales (anxious/depressed; withdrawn/depressed; somatic problems; social problems; thought problems; attention problems; rule-breaking behaviour; and aggressive behaviour). Higher scores reflect more behavioural or emotional problems, and scores ≥65 are considered indicative of clinically significant behaviour problems. For the CDI, a score ≥19 is considered indicative of possible clinical depression and for the BRIEF a score ≥65 is considered indicative of clinical impairment in executive function. For each of these assessments, clinical decline was defined as a >1 SD change in score plus a change in score classification from no impairment at baseline to clinical impairment at follow up. Clinical improvement was defined as a >1 SD change in score plus a change in score classification from clinical impairment at baseline to no impairment at follow up.

Most of the participants in the peginterferon α-2a and ribavirin arm of the PEDS-C trial (86-95%) showed no clinical changes in any of the measures of QoL, behaviour, depression or executive function after 24 weeks of treatment. The exception was mean CHQ Physical summary scores which declined significantly relative to baseline, indicating an overall worsening of the physical aspects of QoL, with eight (15%) of the participants classified as having experienced a clinically significant decline and no participants having experienced a clinically significant improvement (Table 13);

however, the authors noted that the mean CHQ scores at baseline and at 24 weeks were both within the 'average range' (not defined). Three participants (5%) exhibited a clinically significant decline in the depression score, with one being withdrawn from the study due to a suicide gesture, but the majority of participants (95%) exhibited no clinical change in depression scores after 24 weeks.

Table 13 Changes in Quality of life at 24 weeks

QoL outcome	Mean ± SD baseline score	Mean ± SD score at 24-week follow up	Clinically significant improvement, % (n/N)	Clinically significant decline, % (n/N)	No clinical change, % (n/N)	p-value for changes in mean scores
CHQ Physical summary	52.1 ± 4.8	49.8 ± 7.5	0	15 (8/55)	86 (47/55)	0.013 (mean change 2.40 ± 6.8)
CHQ Psychosocial summary	52.1 ± 7.9	52.3 ± 10.2	5 (3/55)	7 (4/55)	88 (48/55)	NR
CBCL Internalising	52.4 ± 8.5	51.0 ± 11.0	4 (2/55)	5 (3/55)	91 (50/55)	NS
CBCL Externalising	50.4 ± 9.4	48.8 ± 10.3	2 (1/55)	5 (3/55)	93 (51/55)	NS
CBCL Total Behaviour Problem	51.5 ± 9.3	49.7 ± 10.2	2 (1/55)	4 (2/55)	95 (52/55)	NS
CDI Total score	5.9 ± 4.2	6.2 ± 5.6	0	5 (3/55)	95 (52/55)	NS
BRIEF Global Executive composite	53.5 ± 9.9	52.2 ± 10.1	5 (3/55)	5 (3/55)	90 (49/55)	NS

NR: not reported; NS: not statistically significant ($p>0.05$)
Scores are for all participants who received peginterferon α-2a in the PEDS-C trial (n=55)[28;54;57]

Long-term follow up of all children who completed 48 weeks of treatment revealed no statistical differences from baseline ($p>0.05$) for any of the outcome measures after one or two years of follow up.[28] Very few children had clinical elevations on the CBCL, none had a clinically high depression score at one year, and only one child had a clinically elevated depression score at the two-year follow up assessment (no further data were presented[28]).

As well as presenting changes in QoL for all participants, the PEDS-C trial reported QoL for a subgroup of 41 participants who achieved a virological response at 24 weeks and continued on peginterferon α-2a and ribavirin for 48 weeks[28] (see full data extraction form in Appendix 4). It should be noted that this subgroup is small and was likely not powered for subgroup analysis so results should be interpreted with caution. Mean subgroup scores for QoL, behaviour, depression and executive function assessed at 48 weeks and 6 months decreased slightly but did not differ significantly from baseline ($p>0.05$). Most of the children did not experience clinically significant changes in physical QoL (83%), internalising behaviours (95%), externalising behaviours (95%) or total behaviour problems (93%) during treatment. Seven participants experienced clinically significant changes in physical QoL. In two cases, scores had returned to baseline levels by the end of treatment. The remaining five participants experienced an early clinical decline that persisted through the end of treatment but in three of these cases the scores had returned to baseline values by the 6-month post-treatment assessment.

Peginterferon α-2b

None of the five studies on peginterferon α-2b reported QoL outcomes.

4.2.8 Growth

Four studies (one peginterferon α-2a[58] and three peginterferon α-2b[48;52;60]) reported whether their participants' height and weight changed during treatment. These studies presented results for the overall study population, not separately for the subgroups of participants who received treatment for 24 or 48 weeks according to HCV genotype. Changes in growth were often presented only in a brief narrative in the publication text without quantitative data and relate to short-term follow-up.

Peginterferon α-2a

One of the two peginterferon α-2a studies (Sokal and colleagues[58]) reported changes in participants' height and weight during treatment. The authors reported that baseline and follow up Z-scores for height were -0.4 ± 1.0 and -0.5 ± 1.1, whilst baseline and follow up Z-scores for weight were -0.3 ± 0.9 and -0.3 ± 1.0. These changes in height and weight from baseline to follow up were not statistically significant.

Peginterferon α-2b

Three of the five peginterferon α-2b studies[48;52;60] reported changes in participants' height and weight during treatment. Pawlowska and colleagues[52] mentioned briefly that there was no influence on height at follow up (24 weeks after treatment) or 2 years after follow up. In the remaining two studies, growth rates decreased during treatment but subsequently recovered. Jara and colleagues[48] observed

that growth during the 48-week period was reduced in 85% of participants (22/26) by 1.6 cm compared with the growth velocity 50th percentile for age and sex (three participants had finished growth before therapy). Growth velocity was entirely normal in the 6-month period after the end of treatment; however, the modest decrease in height percentile observed during therapy was not recovered. Wirth and colleagues[60] observed that 70% of participants (75/107) had a clearly inhibited growth velocity (<3rd percentile) during the treatment phase. Mean growth velocity was 2.47 ± 2.22 cm/year during treatment and increased to 5.73 ± 4.1 cm/year in the follow up period. Mean height percentiles were 50.87 ± 28.89 in the treatment period and 44.25 ± 27.59 at the end of follow up, with mean changes in the height percentile of -7.7 and 1.1 during the treatment and follow up periods respectively. The decrease in mean height percentile during treatment was greater in participants whose treatment duration was longer (n=55, mean 334 days) than in those whose treatment duration was shorter (n=52, mean 155 days) (-11.8 versus -3.6 respectively); however, the statistical significance of these differences was not reported.

The three studies of peginterferon α-2b each reported that their participants lost weight during treatment, and they each classified weight loss as an adverse event. Jara and colleagues[48] observed that 67% of participants (20/30) experienced weight loss, with 23% of the participants (7/30) losing more than 5% of their baseline weight, although weight gain occurred on cessation of treatment. Overall, body weight decreased by 4.8% by week 24 but returned to baseline values by week 48.[48] Pawlowska and colleagues[52] observed that 43% of participants (23/53) experienced weight loss exceeding 10%, with the proportion being lower for treatment naïve children (34.5%, 10/29) than for those previously treated (54.2%, 13/24). Wirth and colleagues[60] reported that 19% of participants (20/107) lost weight, with the mean weight percentiles being 56.57 ± 29.35 in the treatment period and 53.39 ± 29.51 at the end of follow up, which gave a mean change in the weight percentile of -15.5 and 12.3 during the treatment and follow up periods respectively.

4.2.9 Adverse events

Peginterferon α-2a

The incidence of dose discontinuation due to adverse events was reported by both studies of peginterferon α-2a and was relatively low, ranging from 3%[58] to 7%[57] (Table 14).

The incidence of dose modification for any adverse event was reported by both studies of peginterferon α-2a and ranged from 23%[58] to 51%.[57] The most frequent specific events leading to dose modification were neutropenia, which was reported in one study only with an incidence of 17%,[58] and anaemia, which was reported in both studies with incidence rates of 5%[58] to 11%.[57] Dose modification was reported separately for different treatment durations and treatment drugs by Sokal

and colleagues.[58] Dose reduction of peginterferon α-2a occurred in 22% of participants treated for 24 weeks and 23% of those treated for 48 weeks, whilst the incidence of dose reduction of ribavirin due to anaemia in these groups was 0% and 6% respectively, suggestive of a slightly higher risk of ribavirin dose modification with longer treatment duration. These differences were not tested statistically.

Serious adverse events were defined differently in the studies. They occurred at relatively low incidence rates of 4% (considered by the authors as possibly secondary to the drug therapy)[57] and 6% (unclear whether related to the drug therapy).[58] No deaths were reported.

Both trials of peginterferon α-2a reported the incidence of specific adverse events (see full data extractions in Appendix 4 for more details). The most frequent adverse events reported were those typically associated with peginterferon and ribavirin and included flu-like symptoms (54%-91%), headache (45%-62%), injection site reactions (14%-45%), myalgia or arthralgia (12%-36%), irritability (31%-34%) and fatigue (27%-34%). One study reported that gastrointestinal symptoms were relatively frequent (56%)[57] whilst the other study reported a 38% incidence of abdominal pain.[58] The PEDS-C trial[57] reported that 'treatment led to significant declines in total white blood cell counts, absolute neutrophil counts and haemoglobin levels which returned to baseline when therapy stopped' (data were presented in line graphs – not extracted here), but haematological adverse events were not reported by the other study,[58] except where noted as reasons for dose discontinuation or modification (Table 14). Due to the single-cohort nature of the studies, the incidence rates of adverse events were not tested statistically.

Effects of treatment duration on adverse events were reported by Sokal and colleagues.[58] Thyroid hormone problems occurred in 15% of participants who were treated for 48 weeks but did not occur in any of those treated for 24 weeks. The statistical significance of this difference was not reported and the authors did not specify whether this was the only adverse event that differed between the treatment duration subgroups.

Peginterferon α-2b

The incidence of dose discontinuation due to adverse events was reported by two peginterferon α-2b studies and ranged from 1%[60] to 10%.[48] This is similar to the incidence of dose discontinuation reported in the two studies of peginterferon α-2a (3% to 7%) (Table 14).

The incidence of dose modification for any adverse event was not consistently reported in the studies of peginterferon α-2b. No dose modification occurred in the small study by Ghaffar and colleagues.[47] Wirth and colleagues[60] reported that 25% of the participants (27/107) had a dose reduction or

interruption for any adverse event, however their data for dose modification due to specific adverse events suggest that 53% of the participants (57/107) actually experienced a dose modification (Table 14). The most frequent specific events that led to dose modification were anaemia (0%-33% of participants) and neutropenia (12%-23% of participants; but only reported for two of the studies[48;60]). Wirth and colleagues[60] provided separate results for dose modification by age subgroups, showing that older participants (aged 12-17 years) had a higher incidence of dose modification for any reason (35%) than younger participants (aged 3-11 years) (19%), although the difference was not tested statistically.

None of the studies of peginterferon α-2b explicitly defined any of their adverse events as serious or reported any deaths (although one study[60] did mention that no life-threatening or treatment-related adverse events occurred).

All five studies of peginterferon α-2b reported the incidence of specific adverse events (see full data extractions in Appendix 4 for more details), although the types of event that were reported varied among the studies. The most commonly-reported adverse events were the same as those observed in the studies of peginterferon α-2a. Flu-like symptoms and/or fever occurred in all the studies, affecting 66% to 100% of their participants. Other frequent adverse events reported were: headache (45%-67%[48;52;60]), anaemia (11%-33%[46;52;60]), leukopenia (10%-67%,[46;52;60]), neutropenia (17-33%[46;48;60]), myalgia and/or arthralgia (33%-58%[46;48;60]) abdominal pain (21%-43%[48;52;60]), injection site reactions (29%-34%[48;52;60]) and nausea and/or vomiting (27%-45%[48;60]). A limitation to interpreting these findings is that adverse events were not consistently reported in all of the studies and it is unclear how frequent these adverse events would have been in those studies which did not mention them. Due to the single-cohort nature of the studies, the incidence rates of adverse events were not tested statistically.

Differences in the incidence of adverse events with age were reported by Wirth and colleagues, based on subgroups of participants who were aged 3-11 years and 12-17 years.[60] Adverse events that occurred with greater frequency in the older subgroup were blood and lymphatic disorders (30% versus 9%), neutropenia (23% versus 6%) and anaemia (10% versus 4%). The statistical significance of these differences was not reported.

Differences in the incidence of adverse events between previously-treated and treatment-naïve participants were reported by Pawlowska and colleagues.[52] Adverse events that were more frequent in the previously-treated subgroup were flu-like symptoms (79% versus 55%), headache (67% versus 28%), weight loss greater than 10% (54% versus 35%), injection site local reaction (50% versus 21%), abdominal pain (42% versus 3%) and neurasthenia (29% versus 14%). In contrast, thrombocytopenia

was more frequent in the treatment-naïve subgroup (21% versus 8%). The statistical significance of these differences was not reported.

Table 14 Adverse events

Event, % (n/N)	Treatment: PEG α-2a + RBV		Treatment: PEG α-2b + RBV				
	Schwarz and colleagues, 2011[57] n=55	Sokal and colleagues, 2010[58] n=65	Al Ali and colleagues, 2010[46] n=12	Pawlowska and colleagues, 2010[52] n=53	Wirth and colleagues, 2010[60] n=107	Ghaffar and colleagues, 2009[47] n=7	Jara and colleagues, 2007[48] n=30
Dose discontinuation:							
AE	7 (4/55)[a]	3 (2/65)[b]	NR	NR	1 (1/107)	NR	10 (3/30)
Other reason[c]	NR	NR	NR	NR	0 (0/107)	NR	NR
Dose modification:							
Any AE	51 (28/55)[d]	23 (15/65)	NR	NR	25 (27/107)	0 (0/7)	NR
Anaemia	11 (6/55)[d]	5 (3/65)	33 (4/12)	6 (3/53)	7 (7/107)[e]	NR	0 (0/30)
Neutropenia	NR	17 (11/65)	NR	NR	12 (13/107)	NR	23 (7/30)
Weight/growth	NR	NR	NR	NR	10 (11/107)	NR	NR
Other reason	2 (1/55)[d]	6 (4/65)	NR	NR	24 (26/107)	NR	NR
Serious AE	4 (2/55)	6 (4/65)	NR	NR	0 (0/107)[f]	NR	NR
Death	NR	NR	NR	NR	0 (0/107)	NR	NR

AE, adverse event; NR, not reported; PEG α, peginterferon alfa; RBV, ribavirin.
[a]two were considered serious AE; also reported in an abstract[56] that early discontinuation was 4%
[b]both were considered serious AE
[c]excluding discontinuation due to non-response to therapy
[d]reported in an abstract (Schwarz and colleagues[56])
[e]the number of patients with dose modification due to anaemia was stated as 7 and 8 in different places in the original publication[60]
[f]assumed to be zero (authors stated that there were no treatment-related serious AE)

4.2.10 Summary of clinical effectiveness

- Seven studies (two peginterferon α-2a and five peginterferon α-2b) were included - six were single-arm, uncontrolled cohort studies and one was an RCT for which only data for a single-arm met the inclusion criteria. No studies were identified that compared peginterferon alfa to BSC nor peginterferon α-2a versus peginterferon α-2b.
- The studies were relatively small (range 7-107 participants) and of generally poor quality with a potentially high risk of bias (owing to the study design) and little reporting of data/statistical analysis therefore caution is advised in the interpretation of results. The generalisability of the studies to a UK population of children and young people is uncertain.
- SVR rates ranged from 53-66% for peginterferon α-2a and 29-75% for peginterferon α-2b. Excluding two studies with very small participant numbers resulted in a range of 49-65% for peginterferon α-2b.
- For both peginterferon α-2a and peginterferon α-2b, children with genotype 2 or 3 appeared to have higher SVR rates than those with genotype 1 (two peginterferon α-2a and three peginterferon α-2b studies), and children with low viral load at baseline achieved higher SVR rates compared to those with high viral load in three studies (two peginterferon α-2a and one peginterferon α-2b). Where participants were of mixed treatment history (two peginterferon α-2b studies), children who were treatment naïve were more likely to achieve an SVR than those who had been previously treated. The rate of SVR appeared higher in those with normal compared to abnormal ALT levels at baseline (two peginterferon α-2a studies), whilst in one peginterferon α-2b study SVR rates were very similar irrespective of ALT levels. There did not appear to be any impact of the degree of liver fibrosis on SVR rates in the two peginterferon α-2a studies that reported it. It should be noted that numbers of children in some of these subgroups were very small and none of the studies was powered for subgroup analysis, therefore results should be interpreted with caution. In five studies, children with genotype 2 or 3 appeared to have higher SVR rates than those with genotype 1,
- Rates of non-response were variable, ranging from 12-25% (two peginterferon α-2a studies) and 17-51% (three peginterferon α-2b studies). A relapse rate of 17% was reported by one peginterferon α-2a study and a range of 3-17% across four peginterferon α-2b studies.
- No conclusions can be drawn on the effect of treatment on biochemical response (normalisation of ALT levels) (three studies), or histological response (one study), as these were poorly and inconsistently reported.
- In one peginterferon α-2a study, a clinically significant decline was reported in physical health (15% of children) and in the QoL depression score (5%) 24 weeks after starting treatment, but most children showed no clinical changes in any of the measures of QoL,

behaviour, depression or executive function at 24 weeks. For children who completed 48 weeks of treatment, there were no statistical differences from baseline for any of the QoL outcome measures after one or two years of follow up.

- For one peginterferon α-2a study, there were no statistically significant changes in height nor weight from baseline to follow up. For peginterferon α-2b (three studies), there was either no impact on height and weight, or rates decreased during treatment but recovered at the end of treatment or follow-up. The impact on growth was often presented only in a brief narrative so results are not reliable.
- Although not consistently reported, the most frequently occurring adverse events were largely similar across all the studies and were typical of those associated with peginterferon and ribavirin. These included flu-like symptoms, headache, myalgia and/or arthralgia, gastrointestinal symptoms, injection site reactions, anaemia, leukopenia and neutropenia. Serious adverse events occurred at relatively low incidence rates of 4-6% in the two peginterferon α-2a studies that reported them.
- The incidence of dose discontinuation due to adverse events was relatively low and ranged from 3-7% (two peginterferon α-2a studies) and 1-10% (two peginterferon α-2b studies). Dose modifications occurred at a rate of 23-51% (two peginterferon α-2a studies), whilst one small peginterferon α-2b study reported no modifications and one other was unclear due to inconsistent reporting. Adverse events leading to dose modification were usually anaemia and neutropenia.

4.3 SHTAC review of clinical effectiveness in manufacturers' submissions to NICE

Merck Sharp & Dohme (MSD) - peginterferon α-2b and ribavirin

The MSD MS reported a systematic review of clinical effectiveness evidence that was conducted by an independent academic group. The bibliographic databases and search strategies were specified and the searches appear to be reproducible; the study selection, data extraction and quality assessment steps were reported. The MS included eight studies but only presented study characteristics for five of these. The studies included were five non-RCTs of peginterferon α-2b and ribavirin, as well as one RCT and two non-RCT studies of peginterferon α-2a and ribavirin. Of these eight studies in the MS, six met the inclusion criteria for the Assessment Group (AG) report (four on peginterferon α-2b[46;48;52;60] and two on peginterferon α-2a and ribavirin[57;58]). One study of peginterferon α-2b and ribavirin[64] included in the MS was excluded from our AG appraisal because the population age range exceeded the upper limit specified in the scope. The other study (peginterferon α-2a and ribavirin[65]) was excluded from our AG appraisal because of the intervention (participants received non-pegylated

interferon before peginterferon). Conversely, the AG report includes a non-RCT study of peginterferon α-2b and ribavirin[47] that was not included in the MS.

SVR rates in the MS are comparable with those seen in the clinical effectiveness section here, with only minor discrepancies noted in other virological outcomes (in two studies[48;60]). The MS reported briefly on growth inhibition and adverse events and presented results of meta-analyses which pooled data for SVR, EVR, relapse, discontinuation of treatment, and selected adverse events. In addition to the five studies of peginterferon α-2b and ribavirin, some of the meta-analyses also included three studies of peginterferon α-2a and ribavirin. There appears to be moderate to substantial heterogeneity in these meta-analyses, according to the reported I^2 values, but the MS does not provide guidance on interpretation.

Overall, the MSD MS analysis appears reasonably well conducted but the methods of meta-analysis were not reported and interpretation of the meta-analysis results in light of the apparent study heterogeneity is unclear. The MS seems to focus on comparing peginterferon α-2b and ribavirin against peginterferon α-2a and ribavirin, but it is unclear how the RCT and non-RCT evidence was combined in the meta-analysis. The MS concludes that both forms of peginterferon and ribavirin are clinically effective compared to BSC, with no clear differences indicated between the two forms.

Roche - peginterferon α-2a and ribavirin

Roche did not conduct a systematic review of clinical effectiveness evidence (bibliographic databases and search strategies were not specified and insufficient detail was given for the search for evidence to be reproducible). The MS provided results primarily from the PEDS-C trial, plus three other non-RCTs. The processes used for inclusion/exclusion screening, data extraction and quality assessment were not reported, nor were the study details or patient characteristics of the non-RCTs. Two of the four studies, including PEDS-C, are included in the present AG report.[57;58] The remaining two studies do not meet the inclusion criteria for the AG assessment because the population age range exceeded the upper limit specified in the scope,[66] or the trial was retrospective with no details of peginterferon dose or treatment duration.[67]

The MS reported comparative data for both arms of the PEDS-C trial, even though PEG monotherapy is outside the licence and scope. SVR rates in the MS are comparable with those seen in the clinical effectiveness section of the present report. Virological outcomes during treatment (RVR, EVR, EOT) and QoL were not reported in the MS, whilst data on body composition and growth were reported only from those studies that did not meet the inclusion criteria for the AG report. Subgroup analyses for HIV co-infected and re-treated patients were included in the MS using an extrapolation study

carried out using data from four studies for which details are extremely limited. In addition, the numbers of participants are very small.

Overall, the Roche MS appears uncritical and does not provide an explicit interpretation of the clinical evidence. The MS concludes that the PEDS-C trial demonstrates efficacy of peginterferon α-2a and ribavirin over monotherapy (although this comparison is outside the scope of the appraisal). The MS states that there is no safety concern with regard to adverse events; however, only adverse event data from the PEDS-C trial were considered.

4.4 Ongoing studies

No ongoing studies were identified in searches.

5 ECONOMIC ANALYSIS

The aim of this section is to assess the cost-effectiveness of peginterferon alfa and ribavirin in children and young people with chronic HCV.

The economic analysis comprises a systematic review of the literature on the cost-effectiveness of peginterferon alfa and ribavirin treatment; a systematic review of studies of the HRQoL of patients with chronic HCV; a review of the drug manufacturers' submissions to NICE; and an independent economic model and cost-effectiveness evaluation (the SHTAC model).

5.1 Systematic review of existing cost-effectiveness evidence

A systematic review was undertaken in order to identify economic evaluations of peginterferon alfa treatment in children with chronic HCV. A total of 694 references were identified; one conference abstract[68] was identified and retrieved and a further full paper was identified through ad hoc searches and retrieved (see Figure 2).[69] Neither study met the criteria for inclusion (section 3.3) in the systematic review. The full paper[69] investigated non-pegylated interferon treatments in children and was therefore excluded on the grounds of the intervention. The conference abstract[68] did not provide enough detail of methods or results to allow a critical appraisal. Therefore, neither of these studies has been formally quality assessed, however, they are summarised here in terms of the included patient groups, and the assumptions underpinning the economic evaluation, as they provide context for the present review.

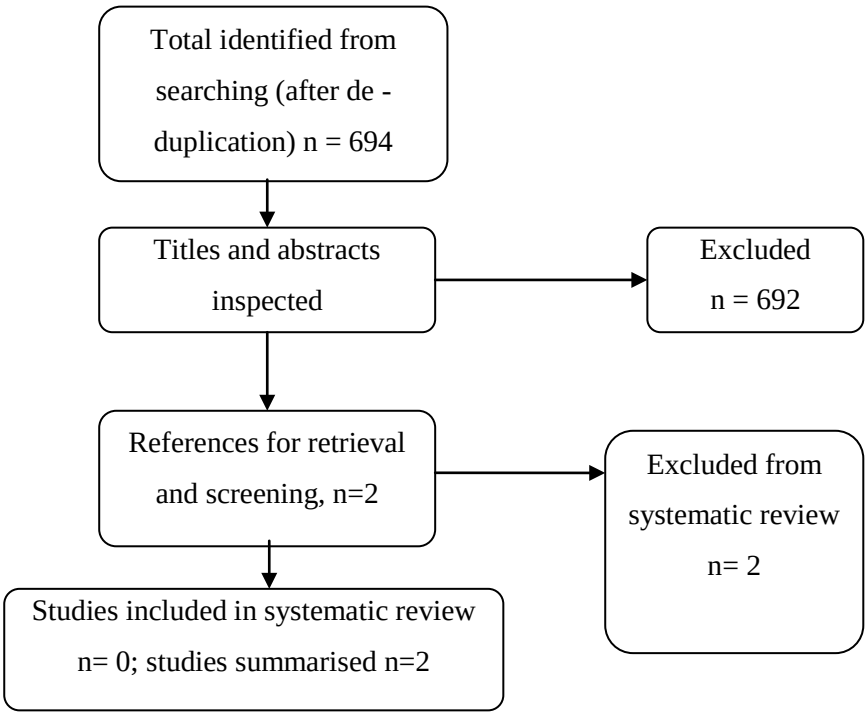


Figure 2 Flow chart for the identification of cost-effectiveness studies

Mernagh and colleagues[68] conducted an economic evaluation in Australia and present this in a conference abstract. Their evaluation was conducted in children receiving a single course of peginterferon α-2b. The treated patient group was compared with an untreated group. Limited information on the patient group is available; however, children and adolescents with a bodyweight of at least 27kg were included as this reflects the lowest dosage allowed in Australia.[68] A lifetime Markov model is the basis for this cost-utility analysis. No detailed information is reported on the assumptions employed in the model. No sources are stated for the natural history, utility, cost or effectiveness inputs except that these were taken from published sources. It is therefore not possible to assess the relevance of this evaluation to the current decision problem. The authors conclude that treatment of HCV with peginterferon α-2b is a cost effective treatment in children, regardless of age. The incremental cost-effectiveness ratio (ICER) presented was reported to be AU$2373 (approximately £1450) per Quality Adjusted Life Year (QALY) gained.

Sinha and colleagues[69] compared a cohort of ten year olds with chronic HCV and no co-infection or co-morbidity, receiving non-pegylated interferon for 6 months or 12 months, compared with no treatment. The perspective of the evaluation was from a societal perspective, and the analysis was undertaken on a USA population basis. A decision tree model was employed for the treatment phase, from where children entered a Markov model in one of three states: non responder, sustained response or no sustained response.[69] The authors state that the natural history of chronic HCV in children is a

prolonged phase with no progression which is delayed until adulthood. Therefore, a latent phase was built into the model, with no transition allowed from their state of chronic HCV to more severe states. In the base case this latent phase was set at 15 years, and varied between zero and 25 years in the sensitivity analysis. Furthermore, the authors state that there is evidence that a higher proportion of paediatric patients will have mild HCV compared with adults, and mild disease is associated with slower progression than severe disease.[69] Therefore, they have assumed that 90% of the cohort would progress at an annual rate of 1% to cirrhosis and that the remaining 10% would progress at a rate of 10%. After transition to cirrhosis, the rate of further complications is similar across the groups. SVR rates were taken from a pooled estimate of rates from five intervention studies, these were 58% for 6 months and 71% for 12 months treatment. Ranges around these were tested in sensitivity analyses. Discounting for costs and outcomes was at a rate of 3%, with sensitivity analysis varying this from 0% to 7%. In this study[69] the alternatives of 'no treatment' and 'treatment for six months' with alfa interferon were both dominated by treatment with alfa interferon for 12 months. This strategy continued to dominate where the cohort age was adjusted to 5 and 15 years of age.[69]

The two studies summarised in this section did not include any assumptions or data that were relevant for the development of the SHTAC economic model.

5.2 Systematic review of health-related quality of life studies

A systematic review was undertaken to assess the HRQoL of people with chronic HCV. The aim of the review was to provide data to populate the lifetime economic model with health state utility values to calculate QALYs. Specifically the aim was to update previous searches for HRQoL in adults[41] and complete full searches for studies in children. For adults, the preferred measure of HRQoL is the EQ-5D[70] and this was used in the previous studies of chronic HCV. We are interested in HRQoL data that are of similar or better quality than used in previous studies and have therefore restricted our searches to those studies using EQ-5D. For children other preference based generic measures were sufficient (Table 15). The search strategies used are described in Appendix 2. The inclusion and exclusion criteria for the review are shown in Table 15.

Table 15 Inclusion/ exclusion criteria for HRQoL of people with chronic HCV

Patients	Children and young people with chronic HCV (aged 3-17 years), including co-infection / previously treated / treatment naïve Adults with chronic HCV including co-infection/ previously treated/ treatment naive (studies dated 2009 onwards)
Study design	Primary study or QoL collected as part of a trial In children: Using generic, preference-based (VAS / TTO /SG) measures such as

	EQ-5D, SF-36 / 6D, HUI In adults: Using EQ-5D (not VAS)
Other	Abstracts excluded if insufficient data available for critical appraisal

VAS: Visual Analogue Scale; TTO: Time Trade Off; SG: Standard Gamble; EQ-5D: EuroQol-5 Dimension; SF-36 / 6D: Short-form 36 or 6D; HUI: Health Utility Index.

The search strategy identified 701 papers in adults and 123 papers in children that were potentially relevant. The titles and abstracts were screened with the full text of nine and five papers retrieved for further inspection for adults and children respectively. After checking the retrieved papers, one adult study met the inclusion criteria.[71] No studies in children were identified. A summary of the selection process and the reasons for exclusion are presented in Figure 3. For children, four studies were excluded because of incorrect QoL measure and one study was an abstract with insufficient detail for critical appraisal. A list of the excluded studies is shown in Appendix 6. An additional study meeting the inclusion criteria in adults was identified from the bibliography of another study.[72] This study had not been identified in the previous reviews of chronic HCV in adults. We therefore included this study in the present review.

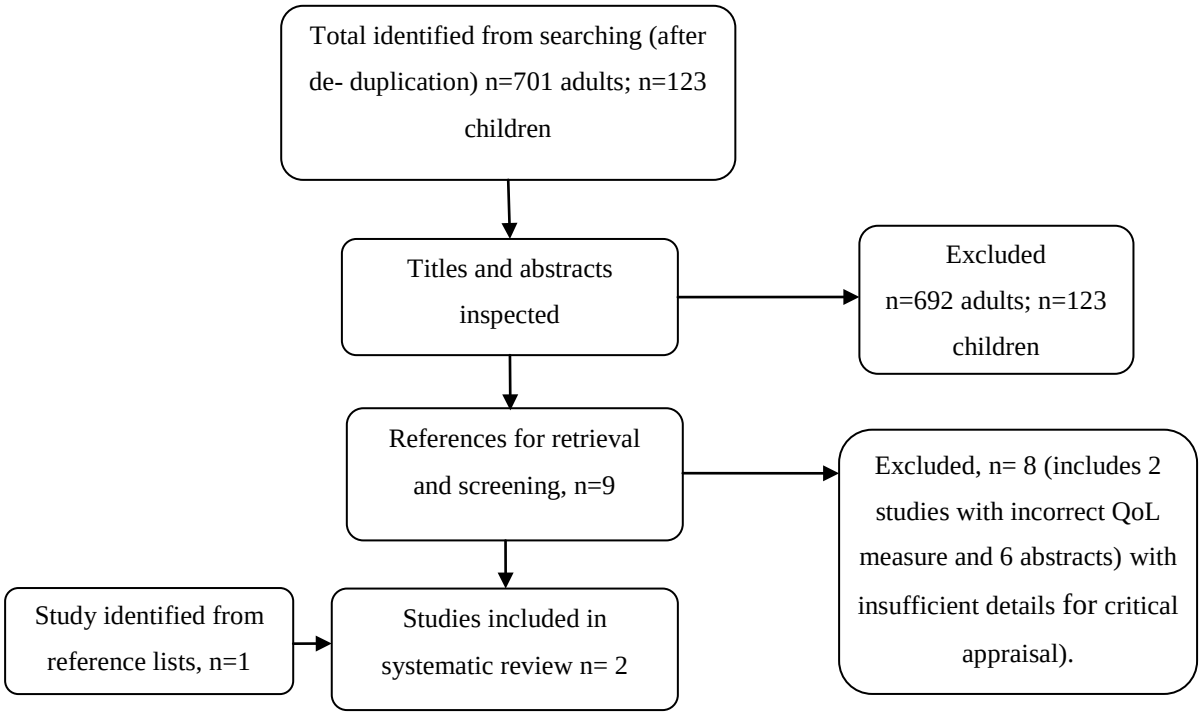


Figure 3 Flow chart of identified studies for HRQoL review in chronic HCV adults and children

Bjornsson and colleagues[71] investigated the HRQoL in patients in different stages of chronic HCV induced liver disease by comparing patients in the mild/moderate fibrosis stage with those with

compensated and decompensated cirrhosis as well as those with SVR. Consecutive patients on regular follow-up were recruited in 16 outpatient clinics in nine different centres in Sweden. Patients were included if they had active or previous HCV infection and were excluded if they had previously undergone a liver transplantation or had life-threatening problems such as hepatocellular carcinoma (HCC). Patients with compensated cirrhosis and decompensated cirrhosis due to aetiologies other than HCV were recruited from a single centre. There were 339 chronic HCV patients (Table 16) and 133 non HCV patients (data not shown here). The study assessed patient HRQoL using the Short form-36 (SF-36) and EQ-5D questionnaires. The present review focuses on the EQ-5D data only.

Across the different cohorts the EQ-5D was shown to vary between 0.656 and 0.811 for decompensated cirrhosis and chronic HCV (mild / moderate fibrosis) respectively indicating poorer HRQoL in those with decompensated cirrhosis ($p<0.001$). The HRQoL in chronic HCV and SVR patients, as measured by EQ-5D index value (Table 16), were similar to that of healthy controls from the Swedish population (reported in the study as being 0.819).

Table 16 Characteristics of included HRQoL study by Bjornsson and colleagues

Indication / disease	Chronic HCV	Compensated cirrhosis	Decompensated cirrhosis	SVR
Participants, n	158	76	53	52
Age, median (IQR)	46 (13)	52 (11)	55 (10)	51 (14)
Sex, %	M 62%; F 38%	M 76%, F 24%	M 71%, F 29%	M 56%, F44%
EQ-5D index value (SD)	0.811 (0.230)	0.749 (0.212)	0.656 (0.266)	0.792 (0.209)

IQR: Interquartile range

Chong and colleagues[72] investigated the HRQoL of a cohort of 193 chronic HCV patients from Canada using a Visual analogue scale (VAS); Standard Gamble (SG); Health Utility Index (HUI); and the EQ-5D. The present review focuses on the data from the EQ-5D only. Consecutive patients in two outpatient centres were recruited and were categorised into seven defined groups based on the stage of their HCV. The different categories were those with no biopsy data, mild/moderate HCV, compensated cirrhosis, decompensated cirrhosis, HCC, transplant, and SVR as seen in Table 17. The number of participants in each group ranged from nine to 44, and the mean age ranged from 44 to 63 years.

The EQ-5D was seen to vary between 0.65 for HCC patients to 0.83 for those with an SVR following treatment with non-pegylated interferon and ribavirin. The authors compared the EQ-5D scores from each of the seven subgroups to the Canadian population norms (0.821, 95% CI 0.810, 0.832) and

these were seen to be statistically significantly different except for the SVR group. In this study[72] the HRQoL was therefore reduced in all participants except those who had been successfully treated. Those with decompensated cirrhosis, HCC, and those who had received a liver transplant had observably lower HRQoL; however this was not statistically analysed. Since publication of the Chong and colleagues study[72] the authors of a UK based study[73] have applied UK social preference weights to the individual patient data for the compensated cirrhosis, decompensated cirrhosis, and HCC data, to produce EQ-5D scores of direct relevance to the UK population. These can be seen in Table 17.

Table 17 Characteristics of included HRQoL study by Chong and colleagues

Chong[72]	**No biopsy**	**Mild / moderate**	**CC**	**DC**	**HCC**	**Transplant**	**SVR**
Participants, n	35	44	24	9	15	30	36
Age, mean (SE)	47 (2.1)	44 (1.5)	57 (2.0)	57 (3.9)	63 (2.7)	54 (1.7)	48 (1.3)
Sex, %	M: 51 F: 49	M: 73 F: 27	M: 29 F: 71	M: 67 F: 33	M: 93 F: 7	M: 70 F: 30	M: 64 F: 36
Mean utility (95% CI)	0.73 (0.62, 0.83)	0.76 (0.68, 0.83)	0.74 (0.66, 0.83)	0.66 (0.46, 0.86)	0.65 (0.44, 0.86)	0.69 (0.62, 0.77)	0.83 (0.77, 0.90)
Mean utility, Thompson Coon[73]	-	-	0.75 (0.66, 0.83)	0.66 (0.46, 0.86)	0.64 (0.44, 0.86)	-	-

CC: Compensated Cirrhosis; DC: Decompensated Cirrhosis: HCC, hepatocellular carcinoma

Both of the included studies assessed the EQ-5D of adults with chronic HCV within different stages of the condition. While the groups were not directly comparable, there were similarities within their case definitions. Some differences can be observed between the estimates from the two studies. In the chronic HCV/mild-to-moderate patients the EQ-5D was seen to be higher in the Bjornsson and colleagues[71] study than in the Chong and colleagues[72] study (0.811 versus 0.76 respectively). In the SVR groups of the two studies the EQ-5D estimates were seen to be higher in the Chong and colleagues[72] study than in the Bjornsson and colleagues[71] study (0.83 versus 0.79 respectively). Rates for compensated cirrhosis and decompensated cirrhosis were seen to be very similar despite the slightly different case definitions used between the two studies. Both of these studies had reasonable sample sizes, although the Bjornsson and colleagues[71] study was larger, and there were fewer categories used in this study, which may, in part, explain the differences observed. Neither of these studies is directly generalisable to the UK population, and both were in adult populations only. Despite this, and in the absence of evidence in children, it would appear that these estimates are

reasonably robust and update estimates previously applied in UK economic evaluations, and as such will be applied in the present economic evaluation (see section 5.4.1 for further details).

5.3 Review of evidence submission from manufacturer to NICE

5.3.1 MSD submission to NICE: cost-effectiveness analysis

Overview

The MSD submission to NICE consists of a written document (containing submitted evidence on the clinical effectiveness and a cost-effectiveness analysis) and a fully executable, electronic copy of the MSD economic model. The MS reports the total costs, the QALYs gained and the cost-effectiveness associated with the treatment of children and young people with chronic HCV with peginterferon alfa (α-2a and α-2b) and ribavirin compared to supportive care. The analysis was conducted from the perspective of the NHS and PSS over a lifetime horizon. The results are presented for several age subgroups and for subgroups relating to HCV genotype.

The MS carried out targeted searches for cost-effectiveness studies for the treatment of paediatric HCV. It found two studies but neither study was relevant to the current decision problem.

Modelling approach

The cost-effectiveness model adopted for the MS is a state transition Markov model that is structurally similar to a published model previously used for adults with chronic HCV.[20;41] The manufacturer's state-transition diagram describing the health states within the model and the allowable transitions between these states is shown in Appendix 8. The model estimates the morbidity and costs resulting from progressive liver disease, and treatment costs. It has a lifetime horizon (until aged 100 years) with a cycle length of 1 year, except for the first year. The model consists of seven non-absorbing health states (SVR, mild HCV, moderate HCV, HCV with compensated cirrhosis, HCC, decompensated cirrhosis and liver transplant) and one absorbing health state of death.

In the first year patients receive treatment for either 12, 24 or 48 weeks depending on the stopping rule and patient genotype. For genotype 2 and 3 patients, the first year was split into two cycles: the first 24 weeks where all patients receive treatment, and the remaining weeks until the end of the year where patients either respond with an SVR or continue with treatment. For genotypes 1 and 4, the first year was split into three cycles: in the first 12 weeks all patients receive treatment, in weeks 13-48 patients remain on treatment only if an EVR was achieved, and in weeks 48-52 responders with an SVR discontinue treatment and those without an SVR continue.

In the absence of child-specific transition probabilities, the adult transition probabilities were used from previous technology appraisals for the treatment of chronic HCV in adults.[20;41] The same transition probabilities were used across all genotypes, in line with these appraisals.

Assumptions

The MS used most of the previous assumptions from the previous HTA model.[20;41] In addition they stated the following assumptions:

- The base case analysis did not take into account spontaneous viral clearance.
- It was assumed that the treatment would discontinue if an EVR (i.e. undetectable HCV-RNA at treatment week 12) was not achieved at week 12.
- Adult transition probabilities (except for the transitions from mild to moderate and from moderate to compensated cirrhosis), utility weights and health state costs (except for SVR state costs) were applied due to the lack of data for paediatric patients.

Critical appraisal of model

The MSD MS was appraised for methodological quality and generalisability to the UK NHS using a checklist adapted from the NICE reference case requirements,[70]and the Philips and colleagues' checklist (Appendix 9).[45] The submission meets all of the requirements for methodological quality and generalisability, except that it did not provide any evidence that the economic model had been validated.

Estimation of effectiveness

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. The effectiveness was derived from a systematic review of the literature for the efficacy of peginterferon alfa and ribavirin. The review identified eight clinical trials in paediatric patients.[46;48;52;57;58;60;64;65] A meta-analysis was then conducted to synthesise the data by genotype (see section 4.3 for limitations with this meta-analysis). The treatment efficacy estimates used in the model are shown in Table 18 and Appendix 8. The MS also uses EVR for genotypes 1/4, where the proportion of patients who achieve EVR is 0.64 and 0.61 for peginterferon α-2a and peginterferon α-2b respectively.

Table 18 Clinical efficacy of peginterferon and ribavirin treatment (MSD MS)

	SVR		
	Proportion	**95% CI**	**Distribution and parameters**

Genotypes 2/3	PEG α-2a + RBV	0.84	0.69-0.95	Beta α=24.82; β=4.73
	PEG α-2b + RBV	0.92	0.80-0.99	Beta α=27.90 β=2.43
Genotypes 1/4	PEG α-2a + RBV	0.52	0.42-0.62	Beta α=49.34; β=45.55
	PEG α-2b + RBV	0.51	0.45-0.58	Beta α=115.37; β=110.85

The trials identified and chosen differ slightly from those in the present clinical effectiveness systematic review. The reasons for the differences and a review of the clinical effectiveness data, presented in the manufacturer submissions, are given in sections 4.3.

Estimation of QALYs

MSD conducted a systematic literature review on the HRQoL of children and young people with HCV that identified four studies; however none of these were considered to be appropriate to be used in the analysis. Adult values were identified as the most appropriate estimates. The utility weights were obtained from previous health technology assessments (see Appendix 8).[20;41] Utilities used in the MSD model can be seen below in the C*ritique of the MS for MSD and Roche* and Appendix 8.

Estimation of costs

The costs included in the model consisted of treatment-related costs including drug acquisition costs, costs associated with treatment initiation and on-treatment and post-treatment monitoring, and health state costs. Costs were based upon previous health technology assessments[20;41] with adjustment to reflect the experience of a child or young person with HCV as advised by experts, and inflated to 2010/2011 prices using the HCHS (Hospital and Community Health Services) Index.[74] Health state costs were used from the previous NICE technology assessments of the treatment of chronic HCV in adults (Appendix 8).[20;41] Health state costs were inflated to 2010/2011 using the HCHS index.[74]

Unit prices for the treatments were obtained from BNF 63.[75] The dosages used were 180 µg/1.73 m^2 per week for pegylated α-2a, 60 µg/m^2 per week pegylated α-2b and 15 mg/kg for ribavirin. The following assumptions were made in order to calculate the treatment cost:

- Ribavirin oral solution: the number of bottles per month was rounded up to the nearest integer
- Ribavirin capsule / tablet: the number of capsules required per day was calculated based on the summary of product characteristics. No wastage was considered.
- Peginterferon α-2a: the number of syringes required per administration was rounded up to the nearest integer (for syringes of 135 or 180 µg).
- Peginterferon α-2b: the number of syringes required per administration was rounded up to the nearest integer (for syringes of 50, 80, 100, 120 or 150 µg).

The treatment cost of a course of peginterferon alfa in combination with ribavirin was:

- Genotypes 2/3 (24 week treatment)
    - Age 3-4: £2,400.00 on peginterferon α-2b
    - Age 5-8: £3,326.20 on peginterferon α-2a; £3,180.42 on peginterferon α-2b
    - Age 9-13: £3,628.06 on peginterferon α-2a; £4,370.16 on peginterferon α-2b
    - Age 14-17: £4,558.02 on peginterferon α-2a; £4,554.80 on peginterferon α-2b
- Genotypes 1/4 (48 week treatment)
    - Age 3-4: £4,800.00 on peginterferon α-2b
    - Age 5-8: £6,652.40 on peginterferon α-2a; £6,360.84 on peginterferon α-2b
    - Age 9-13: £7,256.12 on peginterferon α-2a; £8,740.32 on peginterferon α-2b
    - Age 14-17: £9,116.03 on peginterferon α-2a; £9,109.59 on peginterferon α-2b

Treatment-related costs for treatment initiation, on-treatment and post-treatment monitoring can be seen in the C*ritique of the MS for MSD and Roche* below, and Appendix 8.

Cost-effectiveness results

The MS reports results by age group and genotype, in terms of total costs, life years and QALYs. Table 19 shows the base case results for all patients (aged 5-17 years). Patients receiving peginterferon α-2a, peginterferon α-2b and BSC accrued a total of 19.16, 19.24 and 16.77 discounted QALYs at a cost of £17,798, £17,526 and £22,750 respectively. Both combinations of peginterferon alfa and ribavirin dominated BSC in all patients (5-17 years) and in age and genotype subgroup analyses. Peginterferon α-2b dominated peginterferon α-2a in all patients (5-17 years) and in all subgroup analyses except in patients aged between 9 and 13, and in patients with HCV of genotypes 1/4.

Table 19 Base case results from MSD cost-effectiveness analysis

	versus supportive care						
	Cost (£)	**Life Years**	**QALYs**	**Incremental costs, £**	**Incremental LYG**	**Incremental QALYs**	**ICER (£/QALY)**
Supportive care	£22,750	56.15	16.77	NA	NA	NA	NA
PEG α-2a	£17,798	63.84	19.16	-£4,952	7.69	2.39	Dominates
PEG α-2b	£17,526	64.09	19.24	-£5,224	7.94	2.47	Dominates

The MS conducted deterministic sensitivity analyses (DSA) around structural assumptions (time horizon, discount rates), and the model parameter values. The DSA results showed that peginterferon α-2b dominated BSC in nearly all analyses, except for time horizon and for discount rates. The ICERs

for peginterferon α-2b versus peginterferon α-2a were robust to variation in the model parameters, i.e. peginterferon α-2b dominated peginterferon α-2a for all analyses. The MS probabilistic sensitivity analyses showed that there is a 100% probability that peginterferon α-2a and peginterferon α-2b in combination with ribavirin are cost effective. The cost-effectiveness plane for cost and QALYs for the treatments for the PSA are shown in Figure 4. The cost effectiveness acceptability curve (CEAC) is shown in Figure 5.

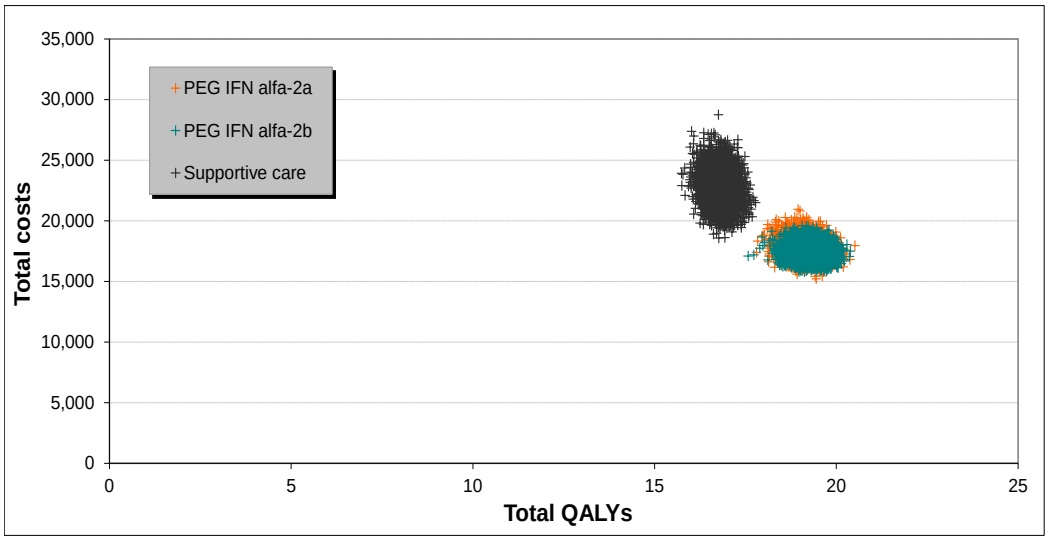


Figure 4 MSD Cost-effectiveness plane for all patients aged 5-17 years

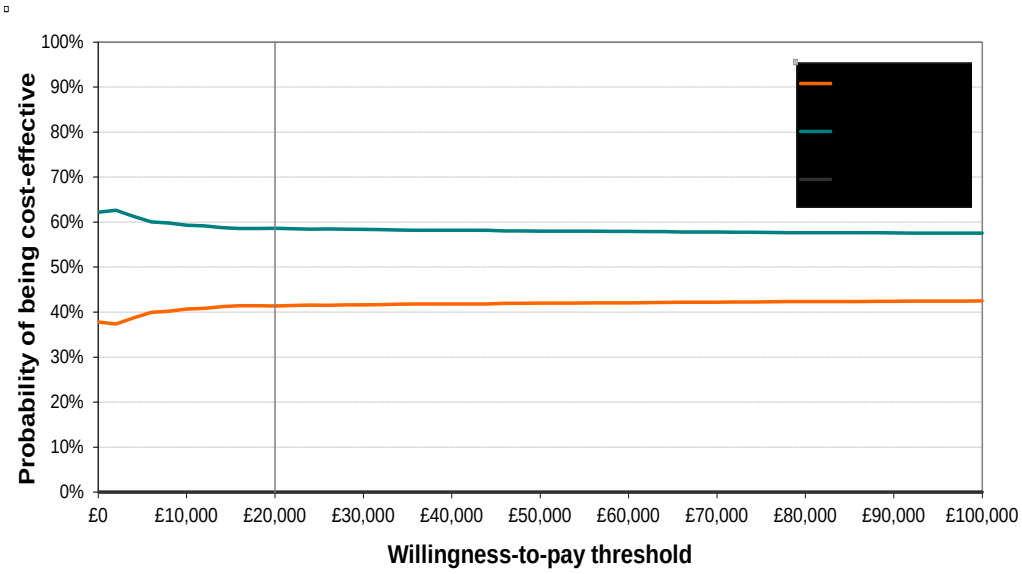


Figure 5 MSD CEAC for all patients aged 5-17 years

Summary of MSD submission

- The MSD model was based upon that developed in previous health technology assessments for chronic HCV in adults.

- The submisison met all but one criterion for methodological quality.
- The model compared peginterferon α-2a with peginterferon α-2b and BSC.
- Treatment efficacy was estimated for SVR as a weighted average of the eight clinical trials for peginterferon α-2a and peginterferon α-2b.
- The base case analysis did not take into account spontaneous viral clearance.
- It was assumed that the treatment would discontinue if an EVR was not achieved at week 12 for genotype 1/ 4.
- Adult transition probabilities (except for the transitions from mild to moderate and from moderate to compensated cirrhosis), utility weights and health state costs (except for SVR state costs) were applied to paediatric patients due to the lack of data.
- A lifetime horizon was used.

5.3.2 Roche submission to NICE: cost-effectiveness analysis

Overview

The Roche submission to NICE consists of a written document (containing submitted evidence on the clinical effectiveness and a cost-effectiveness analysis) and a fully executable, electronic copy of the Roche economic model. The MS reports the total costs, the QALYs gained and the cost-effectiveness associated with the treatment of children and young people with chronic HCV with peginterferon α-2a and ribavirin compared to BSC. The analysis was conducted from the perspective of the NHS over a 30-year time horizon. The results are presented for a baseline population of children aged 11 years with chronic HCV who were treatment-naive and had no co-infection.

Modelling approach

The cost-effectiveness model adopted for the MS is a Markov model that is structurally similar to a published model previously used for adults with chronic HCV.[20;41] The manufacturer's state-transition diagram describing the health states within the model and the allowable transitions between these states is shown in Appendix 8. The model estimates the morbidity and costs resulting from progressive liver disease and treatment costs. It has a time horizon of 30 years with a cycle length of 1 year. The MS comments that the time horizon chosen was considered long enough to capture important costs and effects arising from treatment, as the care pathway is difficult to predict for paediatric patients who are unsuccessful on initial treatment. The base case analysis considers treatment naive patients as reflected in four published clinical trials[57;58;66;67] of peginterferon α-2a and ribavirin. The proportions of participants that enter with mild and moderate chronic HCV (88% and 12% respectively) are based upon a weighted average of data from the four clinical trials. The model consists of seven non-absorbing health states (SVR, mild chronic HCV, moderate chronic HCV,

chronic HCV with compensated cirrhosis, HCC, decompensated cirrhosis and liver transplant) and one absorbing health state of death.

The MS model included a probability of spontaneous SVR for untreated children with chronic HCV, based upon a rapid review they conducted. The results of their rapid review suggested that the probability of spontaneous SVR may vary depending upon how and when the infection was acquired: through vertical transmission at birth or other means during infancy or childhood. From the clinical trial evidence identified,[57;58;66;67] the MS used an average of 70% of patients with vertically acquired chronic HCV and 30% with non-vertically acquired chronic HCV. Those children with vertically transmitted chronic HCV were assumed to only have spontaneous SVR within the first five years and had an annual probability of 2.37% during this time. Similarly, spontaneous SVR was assumed to occur only during the first five years of infection for non-vertically transmitted chronic HCV, with a probability of 1.65%.

Roche conducted a rapid review on the natural history of HCV acquired in childhood. Their review found that observational data from several studies suggest that chronic HCV acquired in childhood progresses more slowly than if acquired in adulthood. They estimated the transition probabilities using a study by Guido and colleagues,[76] a multicentre retrospective study that analysed fibrosis progression and its related risk factors in paediatric chronic HCV. Guido and colleagues[76] found the mean disease duration for paediatric patients with compensated cirrhosis was almost 20 years. For the transitions to more severe health states, such as decompensated cirrhosis, HCC and liver transplantation, adult transition probabilities were used from previous health technology assessments of the treatment of chronic HCV in adults[20;41] (Appendix 8).

Assumptions

The MS used most of the previous assumptions from the previous HTA model. In addition they stated the following assumptions:

- Spontaneous viral clearance was included within the model for untreated patients
- No chronic HCV related costs were assumed to accrue to patients achieving SVR

Critical appraisal of model

The Roche MS was appraised for methodological quality and generalisability to the UK NHS using a checklist adapted from the NICE reference case requirements,[70] and the Philips and colleagues checklist (Appendix 9).[45] The submission meets all of the requirements for methodological quality and generalisability, except that it did not provide any evidence that the economic model had been validated (Appendix 8).

Estimation of effectiveness

Treatment efficacy was estimated for SVR as a weighted average of the four clinical trials for peginterferon α-2a.[57;58;66;67] The weighted average SVR was 59% for genotypes 1/4/5/6 and 89% for genotypes 2/3 with 24 weeks treatment (Table 20 and Appendix 8). The trials identified and chosen differ from those in the present clinical effectiveness review. The reasons for the differences and a review of the clinical effectiveness data, presented in the MTA manufacturer submissions, are given in section 4.3.

Table 20 Clinical efficacy of peginterferon and ribavirin treatment (Roche MS)

	Genotypes 1/4/5/6		**Genotypes 2/3 (48 weeks treatment)**		**Genotypes 2/3 (24 weeks treatment)**
	SVR	Drop-out	SVR	Drop-out	SVR
Weighted average	59%	23%	80%	10%	89%

Estimation of QALYs

Roche conducted a systematic literature review on the HRQoL of children and young people with HCV which identified two partially applicable studies reporting utilities of children with chronic HCV. However, both were based on an expert's Time Trade Off (TTO) values for adults with chronic HCV. Adult values were identified by the MS as the most appropriate estimates. The utility weights were obtained from previous health technology assessments.[20;41] Health state utility values were estimated in a stepwise fashion using a relative effect compared to a baseline utility for the general population. A utility multiplier for the health state was derived by comparing the utility in the literature to the utility of the general population with the same age and gender composition. These utility multipliers were then applied to baseline utilities.

For children under the age of 17 years the economic model applied a baseline utility of 0.95 based on a study by Saigal and colleagues.[77] For the healthy population who are 17 years old and above, the model applied the utilities of adults derived using an algorithm developed by Ara and Brazier.[78] Utilities used in the Roche model can be seen in the C*ritique of the MS for MSD and Roche* and Appendix 8.

Estimation of costs

The model costs consisted of treatment-related costs, including drug acquisition costs, costs associated with treatment initiation and on-treatment and post-treatment monitoring, and health states costs. Unit prices for the treatments were obtained from BNF 63.[75] The doses used in the analysis were in line with the dosing schedule in the relevant clinical trials. Drug costs for peginterferon α-2a were calculated for a dosage of 180 μg/ 1.73 m^2 body surface area (BSA) (max 180 μg) subcutaneously once weekly. Ribavirin (as Copegus) was administered in a dose of 15 mg/kg orally

twice daily (max 1200 mg/day if ≥75 kg and 1000 mg if <75 kg). In the base case the estimated costs for 48 weeks of combination therapy are £8,307.

No syringe sharing was assumed in the model and for all treatments the most efficient vial/syringe to deliver the dose was assumed (i.e. that which produced the least wastage). In other words, if the dose for peginterferon α-2a was estimated to be 125 μg, then one 135 μg pre-filled syringe was used. Similarly, if the dose was estimated to be 137 μg, then the next larger syringe (180 μg) was used.

The economic model incorporated a costing protocol developed as part of a previously developed health technology assessment report[41] to estimate the appropriate evaluation, monitoring and surveillance cost. Health state costs were used from the previous NICE technology assessment of the treatment of chronic HCV in adults[20;41] Costs were inflated to 2010–11 values using the HCHS Pay and Prices Index.[74]

Treatment-related costs for treatment initiation, on-treatment and post-treatment monitoring can be seen below in the *critique of the MS for MSD and Roche* below, and Appendix 8.

Cost-effectiveness results

The MS reports results by genotype, in terms of total costs, life years and QALYs. Table 21 shows the base case results for children aged 11 years. Treating genotypes 1, 4 and 5 patients with peginterferon α-2a and ribavirin improved outcomes by 1.01 QALYs compared to BSC and cost an additional £3,971, which gives an ICER of £3,915. For genotypes 2 and 3, treatment with 24 weeks improved QALYs by 1.57 compared to BSC and cost £1,864 less. For this group, peginterferon α-2a dominates no treatment.

Table 21 Base case results from Roche cost-effectiveness analysis

Treatment	Cost (£)	Life Years	QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Genotype 1, 4 and 5							
No Treatment	£8,199	18.47	14.20	NA	NA	NA	NA
PEG α-2a	£12,170	18.56	15.21	£3,971	0.09	1.01	£3,915
Genotype 2 and 3							
No Treatment	£8,199	18.47	14.20	NA	NA	NA	NA
PEG α-2a, 24 weeks	£6,336	18.61	15.77	-£1,864	0.14	1.57	Dominates no treatment

NA: Not applicable

The MS performed one-way and two way DSAs for the likelihood of SVR, time horizon, discounting, baseline cohort characteristics, rate of disease progression from mild to moderate fibrosis to compensated cirrhosis, probability of SVR with treatment, health state costs, health state utilities, and timing of treatment. The cost-effectiveness of peginterferon α-2a compared to BSC remains below £13,000 per QALY for all analyses. Model results are most sensitive to time horizon, rate of disease progression, probability of SVR with treatment, liver disease at entry, and annual cost of achieving SVR.

In the PSA, for patients with genotypes 2 and 3, there is a 97.2% probability of 24 weeks of combination therapy being cost-effective compared to no treatment at a willingness to pay threshold of £20,000 per QALY. In patients with genotypes 1, 4 and 5 there is a 91.6% probability of being cost-effective at a £20,000 per QALY threshold. The cost-effectiveness planes for cost and QALYs by genotype group are shown in Figure 6. The CEAC is shown in Figure 7.

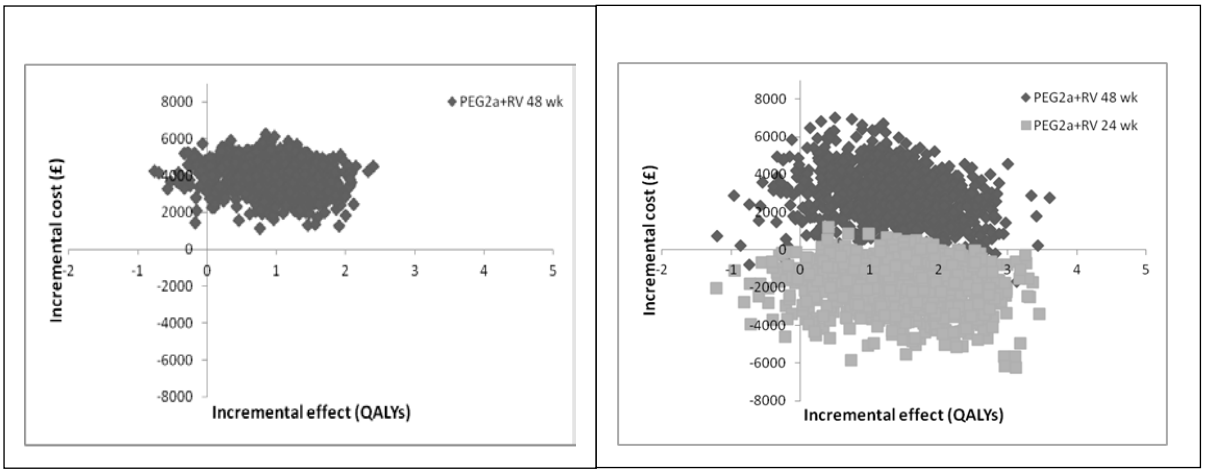


Figure 6 Roche Scatterplots for genotype 1, 4 and 5 (a) and genotype 2 and 3 (b)

a)

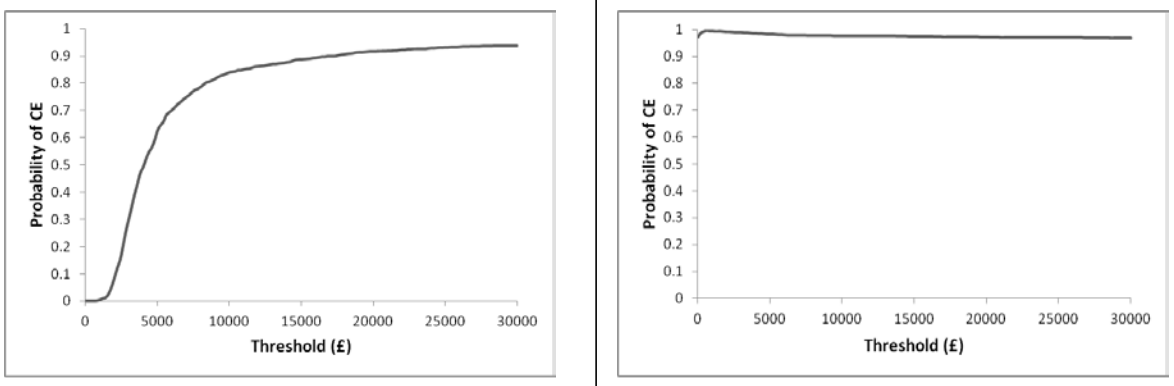


Figure 7 Roche CEAC for genotype 1, 4 and 5 (a) and genotype 2 and 3 (b)

Summary of Roche submission

- The Roche model is based upon that developed for previous health technology assessments of chronic HCV in adults.
- The submission met all but one criterion for methodological quality.
- The model compared peginterferon α-2a with BSC.
- Treatment efficacy was estimated for SVR as a weighted average of four clinical trials for peginterferon α-2a.
- Costs and utilities based upon adult data from previous NICE appraisals.
- Transition probabilities were based upon adult data except for transitions between fibrosis health states, which was based upon a retrospective study in children.
- A 30 year time horizon was used.
- Spontaneous viral clearance was included within the model for untreated patients.
- No chronic HCV related costs were assumed to accrue to patients achieving SVR.
- Health state utility values were calculated using a relative effect of utility found in the literature compared to a utility for the general population with the same age and gender composition. This method assumes that the relative difference in utility between health states is greatest for children than for adults, which appears counterintuitive.

5.3.3 Critique of the MS for MSD and Roche

MSD and Roche used the state transition model applied in previous health technology assessments of peginterferon alfa treatments in adult populations.[20;41] The model structure was considered to be appropriate and was also used in the SHTAC analysis (discussed below) with minor changes to the classification of the health states ‘mild chronic HCV’ and ‘moderate chronic HCV’ (using the METAVIR fibrosis scale F0-F3 according to more recently published evidence).

In the absence of child-specific data, the MSD and Roche MS have used adult data relating to transition probabilities, costs, and utility values. It should be noted that within a longterm model, a large proportion of the time spent in the model would be for when the patient would be an adult, rather than a child, and that these values would therefore be appropriate for most of the duration of the mdoel. In addition, these data were based upon previous health technology assessments which used a systematic approach.[20;41]

As the majority of the patients started in mild chronic HCV, few of these would have been expected to progress to the more severe health states before they reach adulthood. Both the MSD and Roche MS have conducted reviews to estimate the transition probabilities between the mild and moderate and moderate and compensated cirrhosis health states. The transition probabilities for mild to moderate HCV was the same for both MS, and for moderate HCV to compensated cirrhosis these differ between 0.0038 (MSD) to 0.021 (Roche). The transition probabilities differ from those used in the SHTAC model (a summary of these values can be seen in Table 22). The choice of transition probabilities used in the SHTAC model is discussed more fully in subsequent sections.

Table 22 Transition probabilities used in the MS for the HCV health states

From	To	MSD	Roche	SHTAC*
Mild HCV	Moderate HCV	0.014	0.014	0.025
Moderate HCV	CC	0.0038	0.021	0.014

*Values calculated from transition rates between F0 – F1, F1 – F2, F2 – F3, F3 – CC [compensated cirrhosis], where states F0 – F1 are mild HCV, F2 – F3 are moderate HCV

The manufacturers differ in their choice of time horizon. MSD use a lifetime horizon, whilst Roche use a time horizon of 30 years and consider that this horizon is long enough to capture important costs and effects arising from treatment. The appropriate approach for modelling treatments for chronic diseases that affect patients' long term prognoses, as recommended by NICE,[70] is to use the lifetime horizon.

Roche assumes spontaneous SVR for children based upon their review of the literature, whilst MSD does not (as per the previous technology assessments[20;41]). However, it is noted that the probability of spontaneous SVR is small (<2%) in the Roche submission and is unlikely to materially affect the cost-effectiveness results.

The health state utility values applied in the models of the two submissions can be seen in Table 23 and Appendix 8. It can be seen that in both submissions the utility values applied for the mild HCV state, the moderate HCV state, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplant,

post liver transplant and the decrement applied during treatment are the same for both submissions. These were all the utility values applied in the previous adult chronic HCV models with no adjustment made for the present population of children.[20;41] SVR from mild disease differs slightly between the two submissions (0.82 and 0.83 MSD and Roche respectively). Roche do not provide utilities for SVR from moderate disease or compensated cirrhosis and it is unclear from the submission whether the utility weight used for the SVR from mild HCV was also used for these two health states.

Table 23 Utilities applied to the health states in the MSD and Roche submissions

MSD Health State	MSD Utility weight	Roche health state	Roche utility weight
		Healthy children (≤ 16 years old)	0.95
Mild HCV	0.77	Mild disease	0.77
Moderate HCV	0.66	Moderate disease	0.66
Compensated cirrhosis	0.55	Cirrhosis	0.55
SVR from mild HCV	0.82	SVR after mild disease	0.83
SVR from moderate HCV	0.72		
SVR from compensated cirrhosis	0.61		
DC	0.45	Decompensated cirrhosis	0.45
HCC	0.45	HCC	0.45
Liver transplant	0.45		
Post-liver transplant	0.67	Post-liver transplantation	0.67
Disutility due to adverse events	0.11	Treatment for mild disease[a]	0.66
		Treatment for moderate disease[a]	0.55

[a]data used suggest the same utility decrement (0.11) was used

Health state costs used in the MSD and Roche submissions are shown in Table 24 and it can be seen that the majority of costs were the same across the two submissions. Further details of the 95% CI's, distributions and parameters for the MSD submission are given in Appendix 8.

Table 24 Health state costs from the MSD and Roche submission

Health state	MSD Annual costs, £, 2010-11	Roche Annual costs, £, 2010-11
SVR from mild or moderate HCV	£132.18	0
SVR from compensated cirrhosis	£191.11	Not reported
Mild HCV	£178	£178
Moderate HCV	£926	£926
Compensated cirrhosis	£1,469	£1,470

DC	£11,775	£11,780
HCC	£10,492	£10,496
Liver transplant	£47,495	£47,513
Post-liver transplant	£1,788	£1,789

5.4 SHTAC economic evaluation

Overview

We developed a model to estimate the costs, benefits and cost-effectiveness of treatments for chronic HCV for children and young people. The scope for the appraisal, as issued by NICE, states that the interventions to be considered are:

- Peginterferon α-2a with ribavirin
- Peginterferon α-2b with ribavirin.

The comparators for these interventions are BSC, defined in the NICE scope as treatment without any form of interferon treatment, and one another. The perspective of the cost-effectiveness analysis is that of the NHS and PSS. The model estimates the lifelong costs and benefits from each treatment. The costs and benefits were discounted at 3.5% per year, as recommended by NICE.[70] The base price for the costs was taken from the most recently available data (2011-12). The intervention effect in terms of probability of SVR was derived from the systematic review of the clinical effectiveness reported in section 4. The outcome of the economic evaluations is reported as the cost per QALY gained.

Model type and rationale for the model structure

The lifetime model of the natural history of chronic HCV aims to convert the principal outcome of interest in the clinical trials, that is, the probability of SVR, to long term survival outcomes. To estimate the impact of this intermediate effect on final outcomes for patients we required an appropriate model. We adapted our previously published models[20;41] which were used in NICE guidance TA106 and TA200.[33;34] These models were developed for the progression of chronic HCV in adults. Where necessary, they have been modified to reflect the younger patient group in this analysis (discussed in full in subsequent sections). The model has a time horizon of 70 years, as this was considered long enough to capture all relevant costs and benefits, and a cycle length of one year.

The state-transition diagram describing the health states within the model and the allowable transitions between these states is shown in Figure 8. For the current model, we have modified the structure to include health states for the fibrosis states (F0-F4), defined according to the METAVIR scoring system, instead of the previous health states of mild HCV, moderate HCV and compensated

cirrhosis. This is based on more recent evidence on the progression of HCV by Thein and colleagues.[79] They conducted a systematic review of published prognostic rates to determine stage-specific fibrosis progression rates based on a total of 111 studies of individuals with chronic HCV infection (N=33,121). Although many of these studies had retrospective designs the authors meta-analysed studies using both fixed and random effects, provided a number of sensitivity analyses, and adjusted for covariates, and the results were reasonably robust to each of these. We therefore consider that these estimates (see below) are the most reliable data available. These data have allowed improvements to the model to be made, although at the present time not all chronic HCV data required for modelling fully complement these additional health states (see below for discussion of utility and health state costs). The diagram shows nine health states. For clarity, mortality (an absorbing state) has not been included. In this diagram ellipses indicate health states and arrows indicate allowable transitions between health states.

The figure indicates that patients with chronic HCV (F0 – F3) or compensated cirrhosis (F4) may have successful treatment (attain an SVR), remain in their current health state or progress to more severe stages of liver disease. 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 (this is outside the scope of the analysis). Individuals in the SVR health state are assumed to face the same mortality risks as the general population and face no greater risk of HCC than the general population.

For the utility values and health state costs (see below for more detail), the previous health states of mild HCV and moderate HCV were used, where mild HCV relates to F0 and F1, and moderate HCV relates to F2 and F3. Targeted searches, undertaken as part of this assessment, did not identify any other new natural history evidence relating to progression or management of chronic HCV specific to children or young people. Utilities are associated with each health state and for the patient cohort the total number of QALYs is calculated. Patients on treatment with peginterferon alfa have a lower HRQoL than those not on treatment due to adverse events of treatment. This was assumed to be the same decrement for both treatments (see section *health state values / utilities* below).

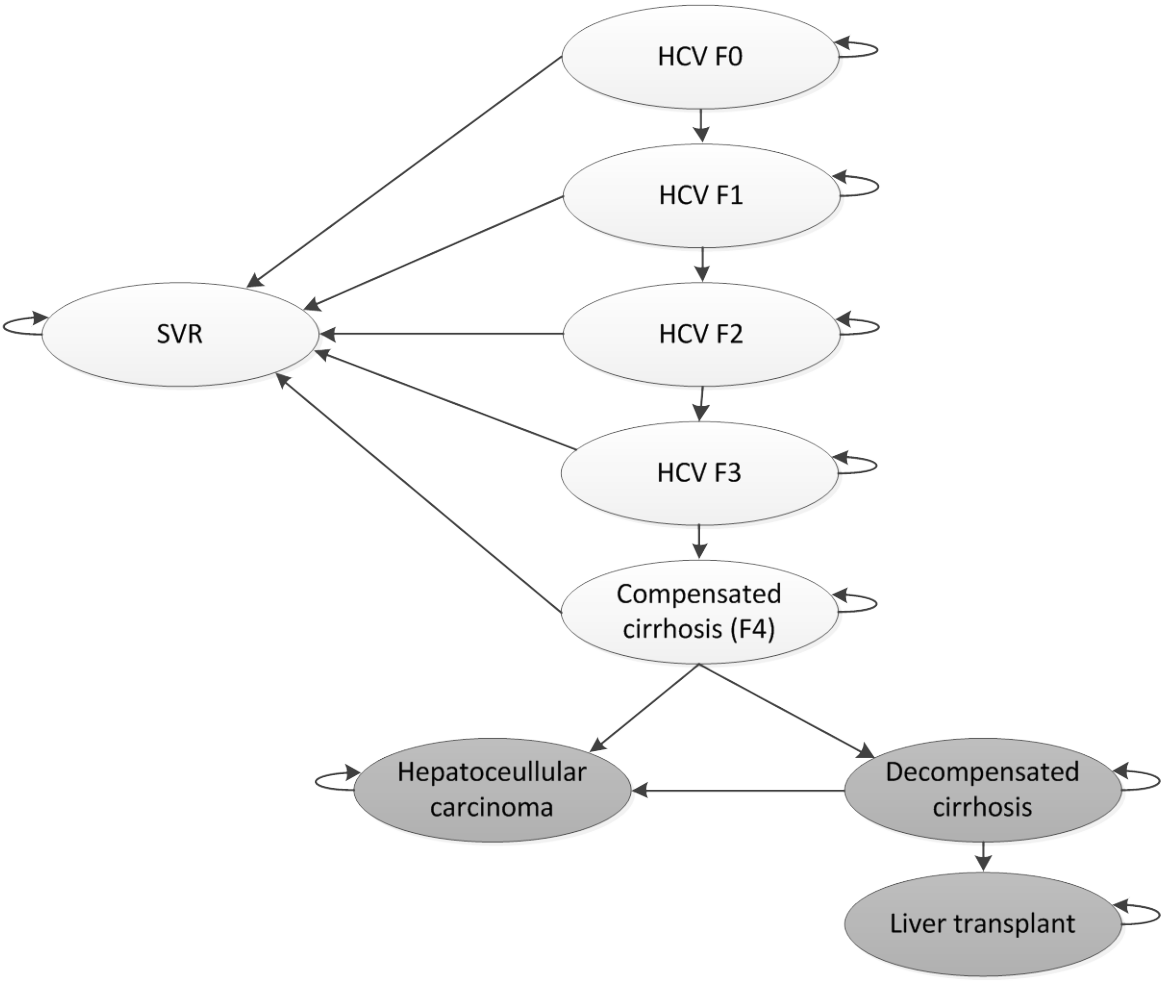


Figure 8 State transition diagram for SHTAC economic model

Patients with chronic HCV (F0-F4) 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 (shown in shaded grey in Figure 4).

Modelling assumptions

We assumed most of the previous assumptions from the previous HTA models. These were:

- That the patient's stage of disease (mild HCV [F0, F1], moderate HCV [F2, F3] and compensated cirrhosis [F4]) prior to treatment influences their subsequent risk of progressive liver disease, post-treatment surveillance and also HRQoL.
- That patients not exhibiting an SVR are expected to face the same risk of disease progression as untreated patients.
- That the same SVR applies for patients with mild or moderate HCV, and for those patients with compensated cirrhosis.

- That the model did not account for re-infection and onward transmission of HCV.
- That the possibility of HCC patients receiving a liver transplant was not considered due to its rarity.
- That discontinuation due to adverse events was not accounted for as it is considered rare.
- That costs associated with the management of adverse events were not accounted for as they were unlikely to be substantial.
- That there is a reduction in utility while patients are being treated with peginterferon alfa and ribavirin.

In addition we included the following assumptions after discussion with our expert advisors:

- The base case analysis assumed that no patients would have spontaneous SVR.
- It was assumed that treatment would discontinue at 24 weeks if an EVR was not achieved at week 12 for genotype 1 or 4.
- Adult transition probabilities, utility weights and health state costs were applied for paediatric patients due to lack of data (discussed in more detail below).
- There is no change to parental utility values. Although there is some suggestion that parental QoL may be reduced the evidence is not sufficient to be applied in the model.

Evaluation of uncertainty

The evaluation of the cost-effectiveness of treatment for chronic HCV in children is based on uncertain information about variables such as the clinical effectiveness, HRQoL and resource use. This uncertainty was evaluated using deterministic and probabilistic sensitivity analyses and scenario analyses. One-way DSA were conducted to evaluate the influence of individual parameters, model structure and assumptions on the robustness of the model (section 5.4.2).

Multi-parameter uncertainty in the model was addressed using PSA (section 5.4.2).[80] In the PSA, probability distributions are assigned to the point estimates used in the base case analysis. The model is run for 1000 iterations, with a different set of parameter values for each iteration, by sampling parameter values at random from their probability distributions. The uncertainty surrounding the cost-effectiveness of the treatment is represented on a CEAC according to the probability that the intervention will be cost effective at a particular willingness to pay threshold. Appendix 10 reports the parameters included in the PSA, the form of distribution used for sampling each parameter, and the upper and lower limits assumed for each variable.

Model validation

The SHTAC model was validated by checking the model structure, calculations and data inputs for technical correctness. The structure is similar to that used in previous health technology assessments[20;41] but was redeveloped to include the health states F0-F4. The SHTAC model was checked for internal consistency against the MS economic models by running the SHTAC model with the inputs used in the MS models. The robustness of the model to changes in input values was tested using sensitivity analyses to ensure that any changes to the input values produced changes to the results of the expected direction and magnitude. Finally, the model results were compared with those from the MS's.

5.4.1 SHTAC data sources

Baseline cohort of chronic HCV children

The baseline characteristics of the modelled populations were taken from the clinical trials used for the effectiveness of the peginterferon alfa treatments. Table 25 shows the initial distribution of patients among fibrosis states based on the studies included in the clinical effectiveness review.[46-48;52;57;58;60]

The included studies use a variety of measures to assess the degree of fibrosis in the participants at baseline. Where possible we have aligned these to relate to the model structure of F0 to F4, and calculated weighted averages to generate the proportion of participants starting within each category. These can be seen in Table 25 and have been applied in the model. The distributions for F0 and F4 are the most reliable because all studies that reported fibrosis at baseline reported the proportion of participants without any fibrosis (F0) and with cirrhosis (F4). The remaining distributions are likely to be subject to some uncertainty because of the different measures used. However, the proportions appear to be in line with those estimated in a systematic review[6] of the natural history of childhood chronic HCV (discussed in Section 1.1) and those of a retrospective study identified on targeted searches of natural history of childhood chronic HCV (Guido and colleagues[76]). Patients eligible for treatment with either peginterferon α-2a or α-2b have a starting age of 11 years, based on the mean ages of those in the clinical trials (Section 4.2).

Table 25 Distribution of patients across stages of disease with different fibrosis system

Source	F0 %	F1 %	F2 %	F3 %	F4* %
All patients	24.6	66.2	7.1	2.1	0

*Compensated cirrhosis

Effectiveness data

Table 26 reports the transition probabilities adopted in the natural history model for the economic evaluation. They represent the transition probabilities for the BSC comparator and are taken from previous health technology assessments,[20;41] except for the transition between the chronic HCV health states. As described above, we have modified the structure to include health states for the fibrosis states (F0-F4), defined according to the METAVIR scoring system, instead of the previous health states of mild, moderate and compensated cirrhosis. The transition probabilities for the transitions between these health states are taken from the random effects meta-analysis of studies included in the systematic review conducted by Thein and colleagues.[79] In addition to these probabilities, there will be a risk of progressing to death, reported below.

Our systematic review of economic evaluations identified one full cost-effectiveness study for treatments of chronic HCV in children.[69] Although not meeting the criteria for inclusion in the present review, as the treatments were not peginterferons, this study suggests that the natural history of chronic HCV in children has a prolonged phase, with progression delayed until adulthood. This was based on expert opinion, and therefore a latent phase of 15 years was built into the model, with no transitions to more severe disease health states allowed. Our targeted searches for natural history identified evidence that disagreed with this assumption. Guido and colleagues[76] analysed fibrosis scores in 112 paediatric patients and found that the progression rate in children was consistent with that in adults. They concluded that disease progression was dependent on duration of HCV infection. It is unclear from the evidence presented whether this was independent of age. Based on the evidence that disease progression is dependent on duration of infection, we concluded that the most appropriate approach is to assume similar transition probabilities between fibrosis states in adults and children as the starting age of children in the cohort is 11 years. We have therefore used the transition probabilities for adults for transitions between the more severe health states, which were taken from the reviews of natural history and/or economic evaluations used previously (See Table 26).

Table 26 Transition probabilities for natural history model

Health state			
From	**To**	**Transition probability (95% CI / SE)[a]**	**Source**
F0	F1	0.117 (0.104, 0.130)	Thein and colleagues[79]
F1	F2	0.085 (0.075, 0.096)	Thein and colleagues[79]
F2	F3	0.120 (0.109, 0.133)	Thein and colleagues[79]

F3	Compensated cirrhosis (F4)	0.116 (0.104, 0.129)	Thein and colleagues[79]
Compensated cirrhosis (F4)	Decompensated cirrhosis	0.039 (0.010)	Fattovich and colleagues[81b]
	Hepatocellular carcinoma	0.014 (0.010)	Fattovich and colleagues[81b]
Decompensated cirrhosis	Hepatocellular carcinoma	0.014 (0.010)	Fattovich and colleagues[81b]
	Liver transplant	0.020 (0.005)	Siebert and colleagues[82b]
	Death	0.130 (0.010)	Fattovich and colleagues[81b]
Hepatocellular carcinoma	Death	0.430 (0.030)	Fattovich and colleagues[81b]
Liver Transplantation	Death	Yr 1 = 0.150 (0.015) Yr 2 = 0.057 (0.005)	Wright and colleagues[83c] Siebert and colleagues[82b]

[a]measure of variance according to published sources
[b]Used in previous health technology assessments[20;41]
[c] No ranges reported, standard error assumed to be mean / 10

Table 27 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 therapies in children taken from studies included in the systematic review of clinical effectiveness (section 4).

As discussed in Section 4.1, no evidence of a comparative nature was identified. Studies included were all single cohort designs. No head to head evidence of effectiveness was therefore available to be used in the economic evaluation of peginterferon alfa compared with BSC, or the evaluation of peginterferon α-2a compared to peginterferon α-2b. In addition data were not suitable for formal indirect comparison owing to the lack of any comparators. A pragmatic approach was therefore taken to use the available evidence through an unadjusted indirect comparison. Caution is recommended in the interpretation of the economic evaluations because there is no means by which the similarity of the included studies can be assessed. For example, participant characteristics, the settings for the studies, and the measurement of the endpoints are not controlled for as they would be in an RCT. Any differences observed in the results of the evaluation may therefore be misleading. Although the use of such an approach has an inherent risk of bias, it does provide an illustration of the likely estimate of cost-effectiveness given the constraints of the data available.

Estimates of the SVR and EVR for total populations and subgroup populations of genotype 1 or 4, and 2 or 3 were estimated using a weighted average approach. Two studies provided data on SVR and EVR for peginterferon α-2a and five for peginterferon α-2b (section 4.2.1). Rates were pooled for the two treatments weighted by the sample size to provide an estimate and an estimated variance that could be used in the economic model. As can be seen in Table 27 the SVR estimates for the two treatments are similar (and confidence intervals around these overlap) and so caution is required when interpreting the outcomes of the model where the point estimates suggest one treatment is more effective than the other.

We assumed that for those receiving BSC, no patients achieved spontaneous SVR, following guidance from our expert advisory group that spontaneous viral clearance after the age of four years is unlikely. In the absence of data, for the base-case analyses, we have assumed that the same SVR applies for all patients with chronic HCV (F0 – F4). This seems a reasonable assumption, given that most patients start in the mild hepatitis health states F0 and F1, and none start in the compensated cirrhosis state (F4). This assumption was also used in previous health technology assessments of adult chronic HCV.[41]

Table 27 Effectiveness input parameters used in SHTAC analysis

Intervention	Genotype	SVR, %	95% CI	EVR, %	95% CI	Source
PEG α-2a + RBV	Overall	60.00	51.23, 68.76	61.67	52.96, 70.36	Schwarz, 2011[57]; Sokal, 2010[58a]
	1 or 4	52.17	40.86, 63.48	57.45	43.31, 71.58	
	2 or 3	85.71	72.25, 98.67	83.33	66.11, 100.5	
PEG α-2b + RBV	Overall	58.37	51.69, 65.05	67.79	61.43, 74.13	Al Ali, 2010;[46] Pawlowska, 2010;[52] Wirth, 2010;[60] Ghaffar, 2009;[47] Jara, 2007[48b]
	1 or 4	50.97	43.09, 58.83	61.04	50.51, 71.56	
	2 or 3	91.43	82.15, 100.7	86.67	74.50, 98.83	

[a]EVR by genotype from Sokal[58] only
[b]SVR by genotype from Pawlowska[52], Wirth[47] and Jara[48] only, EVR by genotype from Wirth[47]
95% CI calculated by reviewers

The distribution of the HCV genotypes in the populations within the studies of peginterferon α-2a and the studies of peginterferon α-2b were different. Grouping these as either genotype 1 or 4, or genotypes 2 or 3, and taking a weighted average approach, it can be seen that in the populations within the studies of peginterferon α-2a 77% would be classed as genotype 1 or 4 and 23% genotype 2 or 3. In the studies of peginterferon α-2b the rates are 82% and 18% for genotype 1 or 4 and genotype 2 or 3 respectively. As evidence suggests that those with genotype 2 or 3 are more likely to respond to treatment, this would suggest that the treatment responses seen in the peginterferon α-2a studies may be better because of the distribution of the genotypes in the baseline populations. A scenario analysis which includes adjusted genotype distributions was undertaken to test the effects of the different

genotype distributions on the base case (see *Scenario analyses: Treatment effectiveness (SVR) peginterferon α-2a versus peginterferon α-2b).*

Health state values / utilities

As discussed in Section 5.2, our systematic review of HRQoL did not identify any studies that assessed the HRQoL in children with chronic HCV. Two studies were identified that assessed HRQoL in adults and in the absence of any health state utility values for children, we decided to derive our base case health state utility values from these studies. The suitability of these data to the current decision problem, and the assumptions made to apply these data to the child population are discussed below, however, these data are consistent with the NICE reference case[70] for measuring and valuing health benefits. HRQoL measurements were undertaken using the EQ-5D, with HRQoL valued using a tariff derived in a general population.[84]

One included study assessed 489 consecutive HCV patients attending outpatient clinics in Sweden.[71] The other assessed the utilities of 193 outpatients at various stages of chronic HCV progression in Canada.[72] The health state utility values from these studies were similar, although slightly different categories of HCV were used in the two studies (see Section 5.2 for further details). In adult models for HCV undertaken in previous health technology assessments utility values were taken from the UK mild chronic hepatitis C trial.[83] The values seen in the two studies identified in the present review are higher than were seen in the UK mild chronic hepatitis C trial. Adult utility weights would be expected to be lower than those in children and young people because comorbidities are known to be fewer in children and general population norms for HRQoL are lower in children. Therefore we have used data from the studies by Bjornnsson and colleagues[71] and Chong and colleagues,[72] rather than the Mild Hepatitis C trial.[83]

The utility values from these studies were seen in Table 16 and Table 17 (Section 5.2) and the utility values used in the SHTAC economic evaluation can be seen in Table 28. Based upon the study of Bjornnson and colleagues,[71] we assumed that there was no difference in the health state utility values between the SVR and mild and moderate HCV (F0-F3) health states and that these were equal to the utility value for the general population. In the absence of data specifically for a moderate HCV disease state in the two included studies we assumed the utility values were the same as the mild to moderate/chronic HCV state because HCV is often asymptomatic for longer in children and young people. For the analysis, we adopted the utility value for the general population for all these health states (0.82).

The two included studies did not report HRQoL for populations undergoing treatment for mild or moderate HCV. We have therefore estimated this using the utility decrement observed between the

untreated and treated participants in the UK Mild Hepatitis C trial and applied this to the utility value (0.82) used in the model for the mild and moderate disease state, assuming that this utility decrement for treatment with peginterferon alfa would be similar for adults and children. The decrement of 0.11 led to a utility of 0.71 for treated mild and moderate children. Utilities for cirrhosis, decompensated cirrhosis, and HCC are taken from the two included studies. For liver transplantation, the estimate from the Chong and colleagues[72] study corresponded with a value used in the previous SHTAC model in adults, which had been taken from a post transplantation study by Ratcliffe and colleagues.[85] In the absence of any data on HRQoL in the post liver transplantation population the utility value used in the previous health technology assessments[20;41] for adult HCV (from Ratcliffe and colleagues[85]) was applied.

Table 28 Health state utilities

Health State	Health state utility value	Decrement vs. SVR	Source
SVR (from mild disease)	0.82	-	Bjornsson and colleagues,[71a]
Mild HCV (F0/F1)	0.82	-	Bjornsson and colleagues,[71a]
Treatment for mild HCV (F0/F1)	0.71	0.11	Mild Hep C trial[83 b]
Moderate HCV (F2/F3)	0.82	-	Bjornsson and colleagues[71a]
Treatment for moderate HCV (F2/F3)	0.71	0.11	Mild Hep C trial[83b]
Cirrhosis (F4)	0.75	0.07	Bjornsson and colleagues[71] Chong and colleagues[72]
Decompensated cirrhosis	0.66	0.16	Bjornsson and colleagues[71] Chong and colleagues[72]
Hepatocellular carcinoma	0.64	0.18	Chong and colleagues[72]
Liver transplantation	0.69[c]	0.13	Ratcliffe and colleagues[85] Chong and colleagues[72]
Post-liver transplantation	0.73	0.09	Ratcliffe and colleagues[85]

[a]Based upon assumption that utility values for SVR, mild HCV and moderate HCV are equal to each other
[b]Treatment decrement in the Mild Hepatitis C trial applied to data
[c]6 months post orthotopic liver transplantation (OLT) used as an estimate of mean utility during the first year post-OLT

To take account of the change in HRQoL over patient lifetimes, we use age-related population norms for HRQoL. As stated above, we assume that the health state utility values for SVR (and HCV states F0 – F3) would be the same as for the general population. For these health states, the health state

utility values are taken from the study by Kind and colleagues,[86] who developed age and gender specific UK EQ-5D population norms (Table 29). We fit these data to give the following:

$$HRQoL = 1.0138 - 0.0033x$$

where x is an individual's age in years.

For all other health states in the model, their health state utility value is calculated by subtracting the health state decrement from the age-related health state utility value (Table 28).

Table 29 Age and gender specific UK EQ-5D population norms from Kind and colleagues[86]

Age band	Male	Female
Under 25	0.94	0.94
25-34	0.93	0.93
35-44	0.91	0.91
45-54	0.84	0.85
55-64	0.78	0.81
65-74	0.78	0.78
75+	0.75	0.71

Cost data

Costs in the model include additional resource use, for example laboratory tests, diagnostic tests and outpatient visits (described as intervention costs), costs relating to the health states used in the model (health state costs), and costs relating to the treatments (drug costs).

Intervention costs

Protocols describing the frequency and intensity of monitoring of patients being treated with peginterferon alfa 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 health technology assessments.[20;41] Costs associated with these protocols were not applied to BSC in the model. The costs of patient management include initial evaluation, assessments of the suitability of treatment, clinical-decision making regarding choice of treatment and final tests prior to commencement of treatment. These costs have been uprated to 2011/12 values (from 2003/04 prices) using the HCHS Pay and Prices Index[74] and are reported in Table 30. The costs used in the model were based upon adult costs, as costs for children were unavailable (a fuller discussion of the possible difference between adult and child costs are given in the *Discussion* section).

The stopping rules for treatment costs for peginterferon alfa have been based on advice from a clinical member of our advisory group, as follows:

- Patients with genotype 1 or 4 receive 48 weeks treatment if they achieve an EVR,
- Patients with genotype 1 or 4 receive 24 weeks treatment if they do not achieve an EVR,
- Patients with genotype 2 or 3 receive 24 weeks treatment.

Table 30 On-treatment monitoring costs by duration of treatment

On-treatment monitoring	Cost (£)
12 weeks	721
16 weeks	869
24 weeks	880
48 weeks	1168
72 weeks	1155

Health state costs

Targeted searches for health state costs for chronic HCV in children did not reveal any relevant studies and so costs were used from the previous health technology assessments for the treatment of chronic HCV in adults.[20;41] Health state costs for SVR, chronic HCV (F0-F3), compensated cirrhosis (F4), decompensated cirrhosis and HCC were taken from the observational study conducted during the UK Mild HCV trial (Table 31) [83] Post-liver transplantation costs were taken from a Department of Health funded study of the costs of liver transplantation.[85] Costs have been updated to 2011/12 costs using the HCHS Pay and Prices Index.[74] Costs for liver transplantation were taken from NHS reference costs for liver transplant (code ref GA01C) for 2010.[87] The health state costs applied for SVR are only applied for the first year after treatment ends.

Table 31 Health state costs

Health state	Cost (£ per year)
SVR	346[a]
Mild chronic HCV (F0/F1)	184[a]
Moderate chronic HCV (F2/F3)	959[a]
Compensated cirrhosis (F4)	1,521[a]
Decompensated cirrhosis	12,193[a]
Hepatocellular carcinoma	10,865[a]
Liver transplantation	32,732[b]
Post Liver transplantation	1,852 [c]

[a] UK Mild HCV trial[83]

[b] NHS reference costs (GA01C)
[c] Ratcliffe and colleagues 2002[85]

Treatment costs

In addition to the health state and health service costs, drug costs also need to be estimated. Drug unit costs were taken from the British National Formulary (BNF), number 64 (September 2012). The average weight, height and body surface area of children by age is shown in Table 32. Body surface area was estimated using the the Dubois formula,[88] as recommended by the BNF.[75]

Table 32 Prescribing for children – child weight, height and body surface area

Age	Weight (kg)	Height (cm)	Body surface area (m^2)[a]
3 years	96	14	0.60
5 years	109	18	0.74
7 years	122	23	0.89
10 years	138	32	1.12
12 years	149	39	1.28
14 years	161	50	1.50

[a]Dubois formula: Body Surface area (m^2) = $0.007184 \times (\text{patient height in cm})^{0.725} \times (\text{patient weight in kg})^{0.425}$

The corresponding prescribing costs for a child of age 11 years are shown in Table 33. Drug costs for peginterferon α-2a (Pegasys) were calculated for a dosage of 100 µg/m^2, administered by patients once per week, corresponding to a weekly cost of £107.76 for a 135 µg pen. The total drug cost for a 24 week course of treatment is £2,586 and for 48 weeks is £5,172. Peginterferon α-2a is used in combination with ribavirin (Copegus) which had a weekly cost of £46.25, and a cost of £1,110 and £2,220 for 24 weeks and 48 weeks respectively. Drug costs for peginterferon α-2b (Virafon Peg) were calculated for a dosage of 60 µg/m^2 per week. This corresponds to a weekly cost of £106.34. The total drug cost for a 24 week course of treatment is £2,552 and for 48 weeks is £5,104. Peginterferon α-2b is used in combination with ribavirin (Rebetol) which had a weekly cost of £62.51, and a cost of £1,500 and £3,000 for 24 weeks and 48 weeks respectively.

Table 33 Prescribing costs using child age of 11 years

Medication	Dose	Cost / Week	Brand name	Total cost	Duration
PEG α–2a	100 µg/m^2 per	£107.76	Pegasys	£2,586	24 weeks

	week			£5,172	48 weeks
PEG α–2b	60 μg/m^2 per week	£106.34	Virafon Peg	£2,552	24 weeks
				£5,104	48 weeks
RBV	15 mg/kg per day	£46.25	Copegus	£1,110	24 weeks
				£2,220	48 weeks
RBV	15 mg/kg per day	£62.51[a]	Rebetol	£1,500	24 weeks
				£3,000	48 weeks

[a] Using oral solution as per the SPC

A discount rate of 3.5% was applied to future costs and benefits.

5.4.2 Results of independent economic analysis

This section reports the cost-effectiveness results for a cohort of eleven year olds with chronic HCV, receiving either peginterferon α-2a or peginterferon α-2b (in combination with ribavirin), compared with BSC and one another. The results for costs and QALYs are presented for each alternative.

The modelled, undiscounted duration in each health state for BSC, peginterferon α-2a and peginterferon α-2b are presented in Table 34. The results show increased survival for both treatments for chronic HCV, when compared with BSC (47.5 years) and a slight survival advantage in patients receiving peginterferon α-2a (57.4 years, compared with 57.1 years in peginterferon α-2b).

Table 34 Summary of undiscounted duration in each health state for BSC, PEG α-2a and PEG α-2b

Health state	BSC (years)	PEG α-2a + RBV (years)	PEG α-2b+ RBV (years)
SVR	0.0	38.2	37.0
F0 - F3	28.6	11.5	12.1
F4	14.5	5.9	6.2
Decompensated Cirrhosis	3.1	1.3	1.3
Hepatocellular carcinoma	0.6	0.2	0.2
Post liver transplant	0.7	0.3	0.3
Total (undiscounted)	47.5	57.4	57.1

The longer duration spent in more severe disease states in children in the BSC cohort is reflected in the health state costs for this group, presented in Table 35. Although this group does not incur treatment costs, the total undiscounted costs are substantially higher for this cohort than either of the

treatment groups, particularly for the cirrhosis and decompensated cirrhosis health states. The additional long term costs for the BSC cohort outweigh the treatment costs of peginterferon α-2a and α-2b. The costs are slightly more for peginterferon α-2b than peginterferon α-2a, for both the treatment and health state costs.

Table 35 Summary of undiscounted costs for BSC, PEG α-2a and PEG α 2b

Cost type (£/patient)	BSC	PEG α-2a + RBV	PEG α-2b+ RBV
Treatment costs overall	£0	£6,481	£7,241
Health State costs			
SVR	£0	£208	£201
F0 - F3	£17,684	£7,103	£7,456
F4	£21,985	£8,956	£9,390
Decompensated Cirrhosis	£38,250	£15,667	£16,420
Hepatocellular carcinoma	£6,027	£2,462	£2,581
Post liver transplant	£3,159	£1,303	£1,365
Total Health State costs	£87,105	£35,699	£37,413
Total costs per patient	£87,105	£42,180	£44,654

The base case results, including discounted total and incremental costs, life years, QALYs, and the ICER for all genotypes are reported in Table 36 for patient cohorts that contain all genotypes. Both peginterferon treatments are cheaper than BSC, with a reduction in costs of between £8,874 (Peg α-2b) and £10,190 (Peg α-2a) over a patient lifetime. Furthermore, both treatments increase the lifetime life years (by 1.82 – 1.88 Life years) and QALYS (by 1.66 – 1.72 QALYs) compared to BSC. Treatment with peginterferon α-2a and peginterferon α-2b dominate BSC, that is they are less expensive and more effective than BSC.

Table 36 SHTAC base case results versus BSC

				Versus BSC			
Treatment	**Costs (£)**	**Life years**	**QALYs**	**Incremental costs, £**	**Incremental LYG**	**Incremental QALYs**	**ICER (£/QALY)**
BSC	£29,245	22.75	20.53				
PEG α-2a	£19,055	24.64	22.25	-£10,190	1.88	1.72	dominates
PEG α-2b	£20,371	24.57	22.19	-£8,874	1.82	1.66	dominates

Base case results for patients with genotypes 1 or 4 only are presented in Table 37 and the results for genotype 2 or 3 are shown in Table 38. The treatment effect (SVR) for genotype 2 or 3 is better than

for genotype 1 or 4, and consequently the results from the model reflect this. There are more additional QALYs accrued in the genotype 2, 3 subgroup (2.52 - 2.68 QALYs) than for the genotype 1,4 subgroup (1.44 – 1.47 QALYs), and more reduction in cost in the genotype 2,3 subgroup (£17,414 - £18,043) than for the genotype 1,4 subgroup (£6,929 - £7,967).

The results for genotype 1 or 4 and 2 or 3 are similar to the base case results, with both peginterferon treatment options cheaper and more effective than BSC, i.e. they dominate BSC.

Table 37 Base case results versus BSC for genotypes 1 or 4

				Versus BSC			
Treatment	**Costs (£)**	**Life years**	**QALYs**	**Incremental costs, £**	**Incremental LYG**	**Incremental QALYs**	**ICER (£/QALY)**
BSC	£29,245	22.75	20.53				
PEG α-2a	£21,278	24.39	22.00	-£7,967	1.63	1.47	dominates
PEG α-2b	£22,316	24.35	21.97	-£6,929	1.60	1.44	dominates

Table 38 Base case results versus BSC for genotypes 2 or 3

				Versus BSC			
Treatment	**Costs (£)**	**Life years**	**QALYs**	**Incremental costs, £**	**Incremental LYG**	**Incremental QALYs**	**ICER (£/QALY)**
BSC	£29,245	22.75	20.53				
PEG α-2a	£11,831	25.45	23.05	-£17,414	2.70	2.52	dominates
PEG α-2b	£11,202	25.61	23.21	-£18,043	2.85	2.68	dominates

The base case results for the comparison of peginterferon α-2a compared with peginterferdon α-2b can be found in Table 39. The results, including discounted total and incremental costs, life years, QALYs, and the ICERs are shown for all genotypes, genotypes 1 or 4 and genotypes 2 or 3. In the overall population base case peginterferon α-2a is slightly cheaper (£19,055 compared with £20,371) and slightly more effective than peginterferon α-2b, (22.25 QALYs compared with 22.19). This leads to peginterferon α-2b being dominated by peginterferon α-2a. In the genotype 1 or 4 sub-population, a similar outcome can be observed, with peginterferon α-2b being dominated. However, for those with genotype 2 or 3, peginterferon α-2b is cheaper and more effective and therefore peginterferon α-2b dominates peginterferon α-2a. This apparent difference illustrates how marginal the differences between treatments are. As stated previously the estimates of effectiveness were very similar based on the included clinical effectiveness studies. These effectiveness estimates predominately drive the

differences in costs and outcomes of the two treatments within the model. This is further explored in subsequent sections.

Table 39 Base case results peginterferon α-2a versus peginterferon α-2b

				Peginterferon α-2b versus peginterferon α-2a			
Treatment	**Costs (£)**	**Life years**	**QALYs**	**Incremental costs, £**	**Incremental LYG**	**Incremental QALYs**	**ICER (£/QALY)**
All genotypes							
BSC	£29,245	22.75	20.53	-	-	-	-
PEG α-2a	£19,055	24.64	22.25	-	-	-	-
PEG α-2b	£20,371	24.57	22.19	£1,316	-0.06	-0.06	dominated
Genotypes 1 or 4							
BSC	£29,245	22.75	20.53	-	-	-	-
PEG α-2a	£21,278	24.39	22.00	-	-	-	-
PEG α-2b	£22,316	24.35	21.97	£1,038	-0.03	-0.03	dominated
Genotypes 2 or 3							
BSC	£29,245	22.75	20.53	-	-	-	-
PEG α-2a	£11,831	25.45	23.05	-	-	-	-
PEG α-2b	£11,202	25.61	23.21	-£629	0.16	0.15	dominates

Notwithstanding the limitations of the evidence base, overall the base case analyses suggest that peginterferon α-2a and peginterferon α-2b are cost-effective compared to BSC. Peginterferon α-2a is cost-effective compared to peginterferon α-2b in the overall population and the subgroup genotype 1or 4, but is not cost-effective compared to peginterferon α-2b in the subgroup with genotype 2 or 3.

Deterministic sensitivity analyses

One-way deterministic sensitivity analyses (DSA) were performed, by varying one parameter at a time, from its base value leaving all other variables unchanged. The sensitivity analysis investigated the effect of uncertainty around the model assumptions, structure, and parameter values on the cost-effectiveness results, in order to highlight the most influential parameters.

Where possible, the parameters were varied according to the ranges of the confidence intervals of these parameters, based on the published estimates, or estimated by reviewers. Where these data were not available an alternative suitable range was chosen. The same ranges were used in the DSA and in probabilistic sensitivity analyses (PSA), (see subsequent section), and these are described in Appendix 10. Due to the large number of parameters, some of the parameters were combined and varied

together, rather than individually, for example for the transition probabilities, health state costs and utility values.

The total costs of the cohort treated with peginterferon alfa are lower than the total costs of the cohort treated with BSC, and QALYs gained are higher (treatment is cheaper and more effective). In the DSA some of the ICERs yielded would be negative which can be difficult to interpret using traditional thresholds for assessing cost-effectiveness as they may appear counterintuitive. For the DSA, results are therefore represented in terms of incremental net benefit (INB), whereby one treatment is more cost-effective (using a willingness to pay (WTP) threshold of £20k) than another if it has a higher net benefit. This approach was used previously in the health technology assessments of shortened treatment duration for hepatitis C[41] and is explained in more detail in Appendix 11. The equation used to calculate INB is:

$$INB = WTP.Q - C$$

where Q is QALY and C is Cost.

The results of the DSA are shown in Table 40 - Table 42 for peginterferon α-2a versus BSC, peginterferon α-2b versus BSC and peginterferon α-2b versus peginterferon α-2a respectively. For all analyses for peginterferon α-2a or peginterferon α-2b compared to BSC, changes to the model parameters and assumptions do not affect the base line results and BSC is dominated by peginterferon α-2a and peginterferon α-2b. The model results are most sensitive to changes in the discount rate, time horizon, the treatment SVR and the baseline fibrosis make-up of the cohort. Changes to the transition probabilities, utility values and health state costs have a relatively small effect on the model results.

For the DSA for peginterferon α-2a versus BSC (Table 40), the ICERs varied between -£581 and -£11,709 (INB £8631 - £223,550). The model results are most influenced by the discount rate chosen, and the incremental costs (-£2,499 to -£44,925) and QALYs (0.58 – 8.93) vary considerably for changes to the discount rate. The previous NICE discount rate (6% costs, 1.5% benefits) produces a more favourable ICER than the current NICE discount rate (3.5% costs, 3.5% benefits). Using a shorter time horizon does not capture all the costs and health benefits. The total additional QALYs for peginterferon α-2a compared to BSC varies between 0.27 and 1.82 QALYs for the 30 and 90 years respectively.

Table 40 Deterministic Sensitivity analyses for pegylated α-2a vs. BSC

	Peg α-2a vs. BSC				
	Incremental Cost	**Incremental QALY**	**INB**	**ICER (£/QALY)**	**ICER (£/QALY)**
Baseline	-£10,190	1.72	£44,616	-£5,920	dominates
Time horizon 30 years	-£3,187	0.27	£8,631	-£11,709	dominates
Time horizon 90 years	-£10,310	1.82	£46,714	-£5,664	dominates
Discount rate 0%	-£44,925	8.93	£223,550	-£5,030	dominates
Discount rate 6% costs, outcomes 1.5%	-£2,499	4.30	£88,515	-£581	dominates
Discount rate 1.5% costs, outcomes 1.5%	-£23,966	4.30	£109,982	-£5,573	dominates
Discount rate 6% costs, outcomes 6%	-£2,499	0.58	£14,060	-£4,324	dominates
SVR Peg 2a 69%	-£12,690	2.00	£52,665	-£6,349	dominates
SVR Peg 2a 51%	-£7,689	1.44	£36,568	-£5,325	dominates
SVR Peg 2b 65%	-£10,190	1.72	£44,616	-£5,920	dominates
SVR Peg 2b 52%	-£10,190	1.72	£44,616	-£5,920	dominates
Cohort 100% F0	-£6,587	1.10	£28,537	-£6,002	dominates
Cohort 100% F2	-£17,242	2.86	£74,428	-£6,030	dominates
Cohort 100% F3	-£19,971	4.23	£104,496	-£4,725	dominates
Cohort 20% F4	-£12,794	2.73	£67,441	-£4,682	dominates
Starting age 5 years	-£11,015	1.81	£47,214	-£6,086	dominates
Starting age 16 years	-£8,718	1.61	£40,949	-£5,410	dominates
Transition probabilities LCI	-£9,399	0.87	£26,750	-£10,834	dominates
Transition probabilities UCI	-£9,491	2.68	£63,090	-£3,542	dominates
Utility values LCI	-£10,190	1.88	£47,776	-£5,422	dominates
Utility values UCI	-£10,190	1.57	£41,685	-£6,471	dominates
Utility values HTA report	-£10,190	3.14	£72,896	-£3,250	dominates
Health state costs LCI	-£6,423	1.72	£40,850	-£3,731	dominates
Health state costs UCI	-£14,466	1.72	£48,893	-£8,404	dominates

INB – incremental net benefit represents the difference between the net benefit of two treatments; LCI: all parameters in this group set at their lower confidence interval; UCI: all parameters in this group set at their upper confidence interval

For the DSA for peginterferon α-2b versus BSC (Table 41), the ICERs varied between -£347 and -£9,720 (INB £7,282 - £215,036). BSC remains dominated in each analysis. As for the results shown

in Table 40, for peginterferon -2a, the model results are also most influenced by the discount rate chosen and the time horizon (see Table 41).

Table 41 Deterministic Sensitivity analyses for pegylated α-2b vs. BSC

	Peg α-2b vs. BSC				
	Incremental Cost	**Incremental QALY**	**INB**	**ICER (£/QALY)**	**ICER (£/QALY)**
Baseline	-£8,874	1.66	£42,068	-£5,347	dominates
Time horizon 30 years	-£2,105	0.26	£7,282	-£8,131	dominates
Time horizon 90 years	-£8,990	1.76	£44,096	-£5,122	dominates
Discount rate 0%	-£42,451	8.63	£215,036	-£4,919	dominates
Discount rate 6% costs, outcomes 1.5%	-£1,440	4.15	£84,503	-£347	dominates
Discount rate 1.5% costs, outcomes 1.5%	-£22,191	4.15	£105,255	-£5,343	dominates
Discount rate 6% costs, outcomes 6%	-£1,440	0.55	£12,530	-£2,597	dominates
SVR Peg 2a 69%	-£8,874	1.66	£42,068	-£5,347	dominates
SVR Peg 2a 51%	-£8,874	1.66	£42,068	-£5,347	dominates
SVR Peg 2b 65%	-£10,819	1.88	£48,328	-£5,769	dominates
SVR Peg 2b 52%	-£7,207	1.47	£36,702	-£4,887	dominates
Cohort 100% F0	-£5,391	1.06	£26,534	-£5,100	dominates
Cohort 100% F2	-£15,691	2.75	£70,789	-£5,696	dominates
Cohort 100% F3	-£18,329	4.08	£99,854	-£4,496	dominates
Cohort 20% F4	-£11,391	2.64	£64,141	-£4,319	dominates
Starting age 5 years	-£11,703	1.75	£46,610	-£6,705	dominates
Starting age 16 years	-£7,886	1.55	£38,957	-£5,076	dominates
Transition probabilities LCI	-£8,110	0.83	£24,797	-£9,720	dominates
Transition probabilities UCI	-£8,199	2.59	£59,925	-£3,170	dominates
Utility values LCI	-£8,874	1.81	£45,100	-£4,899	dominates
Utility values UCI	-£8,874	1.52	£39,255	-£5,842	dominates
Utility values HTA report	-£8,874	3.03	£69,414	-£2,932	dominates
Health state costs LCI	-£5,233	1.66	£38,426	-£3,153	dominates
Health state costs LCI	-£13,008	1.66	£46,201	-£7,837	dominates

INB – incremental net benefit represents the difference between the net benefit of two treatments; LCI: all parameters in this group set at their lower confidence interval; UCI: all parameters in this group set at their upper confidence interval

The DSA for peginterferon α-2b versus peginterferon α-2a are shown in Table 42. The DSA should be treated with caution due to uncertainty around the relative treatment effect for SVR for peginterferon α-2b versus peginterferon α-2a. The model results are most sensitive to changes in the treatment effectiveness. Peginterferon α-2b continues to be dominated by peginterferon α-2a for all changes to the model parameters except for changes to the SVR (pegylated α-2a 51% or pegylated α-2b 65%, shown in bold in the Table 42) and the starting age of the cohort (age 5 years).

Table 42 Deterministic Sensitivity analyses for pegylated α-2b vs. pegylated α-2a

	Peg α-2b vs. Peg α-2a				
	Incremental Cost	**Incremental QALY**	**INB**	**ICER (£/QALY)**	**ICER (£/QALY)**
Baseline	£1,316	-0.06	-£2,549	-£21,345	dominated
Time horizon 30 years	£1,082	-0.01	-£1,349	-£81,135	dominated
Time horizon 90 years	£1,320	-0.06	-£2,619	-£20,323	dominated
Discount rate 0%	£2,474	-0.30	-£8,513	-£8,191	dominated
Discount rate 6% costs, outcomes 1.5%	£1,059	-0.15	-£4,012	-£7,176	dominated
Discount rate 1.5% costs, outcomes 1.5%	£1,775	-0.15	-£4,728	-£12,024	dominated
Discount rate 6% costs, outcomes 6%	£1,059	-0.02	-£1,530	-£45,016	dominated
SVR Peg 2a 69%	£3,816	-0.34	-£10,597	-£11,256	dominated
SVR Peg 2a 51%	-£1,185	0.22	£5,500	-£5,491	**dominates**
SVR Peg 2b 65%	-£629	0.15	£3,711	-£4,082	**dominates**
SVR Peg 2b 52%	£2,983	-0.25	-£7,914	-£12,097	dominated
Cohort 100% F0	£1,196	-0.04	-£2,003	-£29,626	dominated
Cohort 100% F2	£1,551	-0.10	-£3,639	-£14,852	dominated
Cohort 100% F3	£1,642	-0.15	-£4,642	-£10,946	dominated
Cohort 20% F4	£1,403	-0.09	-£3,300	-£14,783	dominated
Starting age 5 years	-£687	-0.06	-£605	£10,641	£10,641
Starting age 16 years	£831	-0.06	-£1,991	-£14,339	dominated
Transition probabilities LCI	£1,289	-0.03	-£1,953	-£38,855	dominated
Transition probabilities UCI	£1,292	-0.09	-£3,164	-£13,809	dominated
Utility values LCI	£1,316	-0.07	-£2,676	-£19,345	dominated
Utility values UCI	£1,316	-0.06	-£2,430	-£23,625	dominated

Utility values HTA report	£1,316	-0.11	-£3,482	-£12,151	dominated
Health state costs LCI	£1,190	-0.06	-£2,423	-£19,308	dominated
Health state costs LCI	£1,458	-0.06	-£2,691	-£23,657	dominated

INB – incremental net benefit represents the difference between the net benefit of two treatments; LCI: all parameters in this group set at their lower confidence interval; UCI: all parameters in this group set at their upper confidence interval

Overall it appears that the results are robust to changes in the model assumptions, the structure and the input parameters.

Scenario analyses

In addition to the sensitivity analyses three scenario analyses were undertaken to investigate the uncertainty around structural assumptions. The first investigated a range of estimates for the SVR as those used in the base case analysis were based on pooled estimates from cohort studies included in the review of clinical effectiveness and are therefore subject to uncertainty. The second varied the rate of progression of the cohort to the cirrhosis disease state and the final scenario assessed the impact of delaying treatment until adulthood (referred to as 'watchful waiting') rather than treating with peginterferon alfa during childhood.

1) Treatment effectiveness (SVR) of peginterferon α-2a versus peginterferon α-2b

For the base case analysis (reported above in Table 39) the SVR for peginterferon α-2b is slightly lower (58%) than for peginterferon α-2a (60%) and this results in an increased cost of £1316 and reduced QALYs (-0.06). In this case, peginterferon α-2a dominates peginterferon α-2b (i.e. is the optimal treatment strategy).

Table 43 shows the cost-effectiveness results of peginterferon α-2b compared to peginterferon α-2a using a range of estimates for the SVR for peginterferon α-2b. These estimates of SVR for peginterferon α-2b are varied between 50% and 70%, whilst keeping the SVR estimate for peginterferon α-2a at 60% for all analyses.

The cost-effectiveness of peginterferon α-2a compared to peginterferon α-2b is proportionate to the relative SVR of these treatments. For strategies where SVR for peginterferon α-2a is greater than or the same as for peginterferon α-2b, peginterferon α-2a is the optimal treatment and conversely where SVR for peginterferon α-2b is greater than for peginterferon α-2a, peginterferon α-2b is the optimal treatment. This demonstrates the extent of the uncertainty in the base case results.

As noted above, in the base case analysis the SVR for peginterferon α-2b is slightly lower (58%) than for peginterferon α-2a (60%). However, there is uncertainty about the reliability of the relative SVR

effect sizes between peginterferon α-2a and peginterferon α-2b, due to the poor quality of the studies and the lack of head-to-head trials. Furthermore the SVR study estimates range from 53-66% in children treated with peginterferon α-2a and 49-65% for those treated with peginterferon α-2b when excluding the two studies with very small participant numbers, and this further demonstrates the variance around the estimates in the study samples.

As noted above, for the base case analysis the SVR for peginterferon α-2b is slightly lower (58%) than for peginterferon α-2a (60%). This SVR for each treatment for each study is influenced by the population genotype distribution. As noted above, the distribution of the HCV genotypes in the populations within the studies of peginterferon α-2a and the studies of peginterferon α-2b were different. Within the studies of peginterferon α-2a, 77% would be classed as genotype 1 or 4 and 23% genotype 2 or 3. In the studies of peginterferon α-2b the rates are 82% and 18% for genotype 1 or 4 and genotype 2 or 3 respectively. As evidence suggests that those with genotype 2 or 3 are more likely to respond to treatment, this would suggest that the treatment responses seen in the peginterferon α-2a studies may be better because of the distribution of the genotypes in the baseline populations. We adjusted the SVR treatment response for peginterferon α-2a and α-2b, by assuming the same genotype distributions for both treatments (80% genotype 1 or 4, 20% genotype 2 or 3). In this scenario, the SVR treatment response for both treatments was 59%. In this scenario, both treatment cohorts have the same total QALY (22.22), and peginterferon α-2a (£19,333) has a slightly lower cost than peginterferon α-2b (£20,093).

Table 43 Scenario analysis of peginterferon α-2b versus peginterferon α-2a

SVR		Peg α-2b		Peg α-2b Incremental		ICER (£/QALY)	Optimal treatment
Peg α-2a	Peg α-2b	Cost, £	QALYs	Cost, £	QALYs		
60%	58%[a]	£20,371	22.19	£1,316	-0.06	dominated	Peg 2a
60%	50%	£22,594	21.94	£3,539	-0.31	dominated	Peg 2a
60%	55%	£21,205	22.10	£2,149	-0.15	dominated	Peg 2a
60%	60%	£19,815	22.25	£760	0.00	NA	Peg 2a
60%	65%	£18,426	22.40	-£629	0.15	dominates	Peg 2b
60%	70%	£17,037	22.56	-£2,018	0.31	dominates	Peg 2b

For all analyses with SVR of 60% for Peg α-2a, the total cost is £19,055 and the total QALYs are 22.25
[a] base case analysis
NA: not applicable

2) Progression of hepatitis to cirrhosis

We conducted a scenario analysis varying the progression rate to cirrhosis (F4). In the base case the patients with BSC spent a mean duration of 28.65 years in the chronic HCV health states (F0-F3), see

Table 34. The base case transition probabilities between the health states ranging between F0 (no cirrhosis) and F3 (compensated cirrhosis) were all in the region of 0.1 (Table 26). For the scenario analysis we varied the transition probabilities between the fibrosis states from 0.05 to 0.3, with the same probability for transitions between each of these states (F0-F4).

Table 44 shows the effect of varying these transition probabilities on the comparison of pegylated α-2a versus BSC. The time spent in the chronic HCV health states varies between 10 and 48 years, and for all analyses the total costs for the BSC cohort are more than for the peginterferon α-2a group and the total QALYs are lower, i.e. peginterferon α-2a dominates BSC. Therefore treatment with peginterferon α-2a is likely to be cost-effective with a greater or lesser degree of time spent in the chronic HCV health state. These analyses have been completed using treatment with peginterferon α-2a; however the same would also be true for analyses completed using treatment with peginterferon α-2b.

The natural history of chronic HCV acquired in infancy is not well understood and there is some uncertainty around the rate of progression to cirrhosis and more severe liver disease. Guido and colleagues[76] estimated the mean time from infection to cirrhosis was 28 years, based upon a median fibrosis progression rate of 0.142. They considered that this was consistent with the duration observed for adults of 30 years. The transition probabilities between fibrosis states estimated by Guido and colleagues were higher than the transition probabilities used in our model (from Thein and colleagues[79]) and so the duration in the chronic HCV states in our model was longer than estimated by Guido and colleagues.[76] However, we note that the study by Thein and colleagues,[79] although using an adult population, is a far larger study (N=33,121) than the study by Guido and colleagues (N=112).[76]

Table 44 Scenario analysis for time to progression to cirrhosis health state

Transition probability	Time years	BSC		PEG α-2a		ICER (£/QALY)
		Cost, £	QALYs	Cost, £	QALYs	
Base Case	28.65	£29,245	20.53	£19,055	22.25	Peg 2a dominates
0.05	48.57	£19,797	22.65	£15,091	23.16	Peg 2a dominates
0.10	30.20	£29,157	20.75	£19,021	22.35	Peg 2a dominates
0.15	20.69	£34,597	19.25	£21,290	21.71	Peg 2a dominates
0.20	15.59	£37,954	18.17	£22,690	21.25	Peg 2a dominates
0.30	10.42	£41,859	16.78	£24,321	20.65	Peg 2a dominates

3) Watchful waiting

We investigated a scenario of treating patients with peginterferon α-2a as children (aged 11 years) compared with a 'watchful waiting' scenario where patients are treated only once they are adults (aged 18-30 years). The results are shown in Table 45. These show that strategies for watchful waiting cost more and are associated with a reduced QALY compared with treating as a child (i.e. treating children strategy dominates watchful waiting). For example, treating adults aged 21 years would be associated with an increased cost of £3,872 and decreased QALY of 0.07 compared with treatment at age 11 years.The potential disbenefit from delaying treatment until aged 30 is even greater with a decreased QALY of of 0.45 QALYs, due to the progressive nature of the disease many of these patients would have reached more severe disease by this age. These analyses have been completed using treatment with peginterferon α-2a, however the same would also be true for analyses completed using treatment with peginterferon α-2b.

Table 45 Scenario for watchful waiting

Results	Costs	Life Years	QALY	Incremental Cost	Incremental QALY	ICER (£/QALY)
PEG α-2a	£19,055	24.64	22.25			
WW 18	£21,959	24.62	22.22	£2,904	-0.02	-£140,104
WW 21	£22,928	24.56	22.17	£3,872	-0.07	-£53,662
WW 25	£24,476	24.43	22.04	£5,420	-0.20	-£26,962
WW 30	£26,668	24.19	21.79	£7,612	-0.45	-£17,095

WW: watchful waiting

Probabilistic sensitivity analysis

In addition to the DSA and scenario analyses, a PSA was undertaken. Parameters were sampled probabilistically from appropriate distributions: these included the proportions of children distributed across genotypes, the transition probabilities, the health state utilities and monitoring, health state and treatment costs. Details of the PSA and the distributions applied are reported in Appendix 10. One thousand simulations were run. A summary of the results from the PSA are shown in Table 46.

Table 46 SHTAC base case PSA results

Treatment	Costs (£) (IQR)	QALYs (IQR)	vs. BSC	vs. PEG α-2a
			ICER (£/QALY)	ICER (£/QALY)
BSC	£29,689 (£26,958 -£31,979)	20.50 (20.1 – 21.0)	-	-
PEG α-2a	£19,226 (£17,679 - £20,593)	22.22 (22.0 – 22.5)	dominates	-
PEG α-2b	£20,558 (£19,202 - £21,777)	22.16 (21.9 – 22.4)	dominates	dominated

IQR – interquartile range shows the range between the 25% and 75% percentiles

The PSA results closely reflect those from the deterministic base case results; the total costs for peginterferon α-2a and peginterferon α-2b, (£19,226 and £20.558 respectively) are both cheaper than those incurred by patients receiving BSC (£29,689). Patients in the BSC group also accrue fewer QALYs than their counterparts in both treatment groups; 20.5 compared with 22.22 with peginterferon α-2a and 22.16 with peginterferon α-2b. Therefore, in the PSA peginterferon α-2a and peginterferon α-2b both dominate BSC. Peginterferon α-2a is again cheaper and more effective than peginterferon α-2b in this analysis, and dominates this treatment.

The scatter plots for cost and health outcomes for the treatment options for the PSA are shown in Figure 9. The CEAC is shown in Figure 10, and indicates that at all WTP thresholds, peginterferon α-2a has the highest probability of being cost effective. At a WTP threshold of £20,000 and £30,000 per QALY, the probability of being cost-effective is 68% and 66% for peginterferon α-2a and 32% and 34% for peginterferon α-2b respectively.

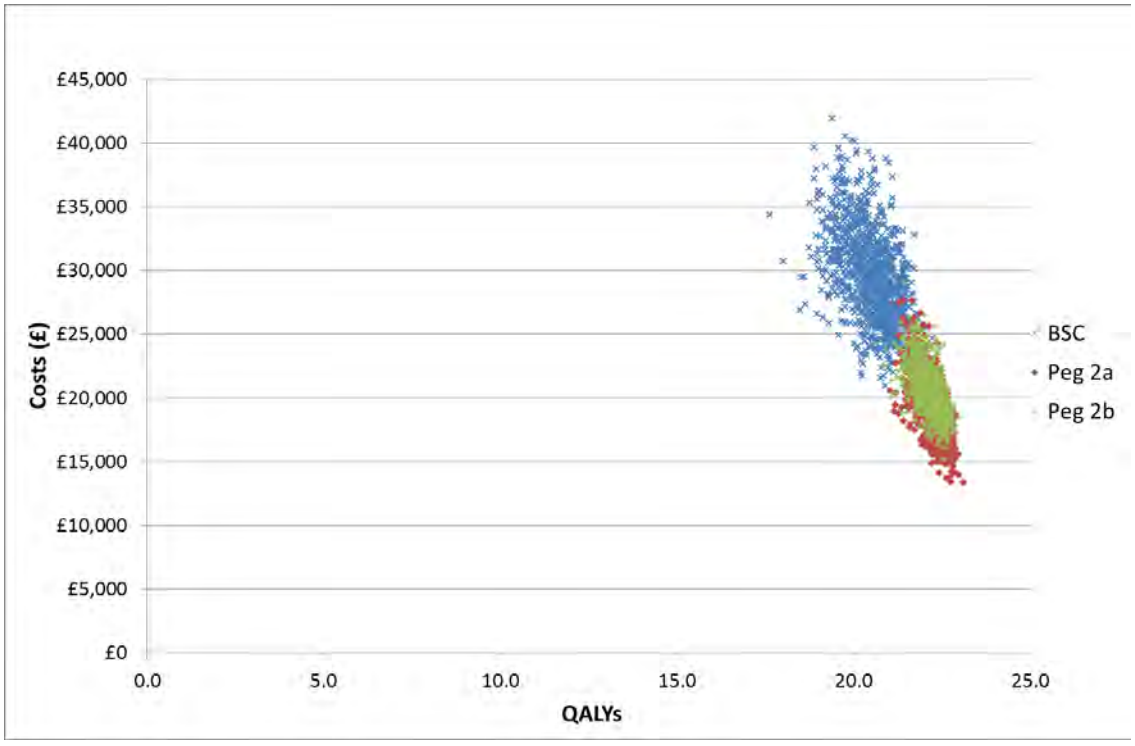


Figure 9 Scatterplot of the costs and health benefits for PEG α 2a, PEG α-2b and BSC

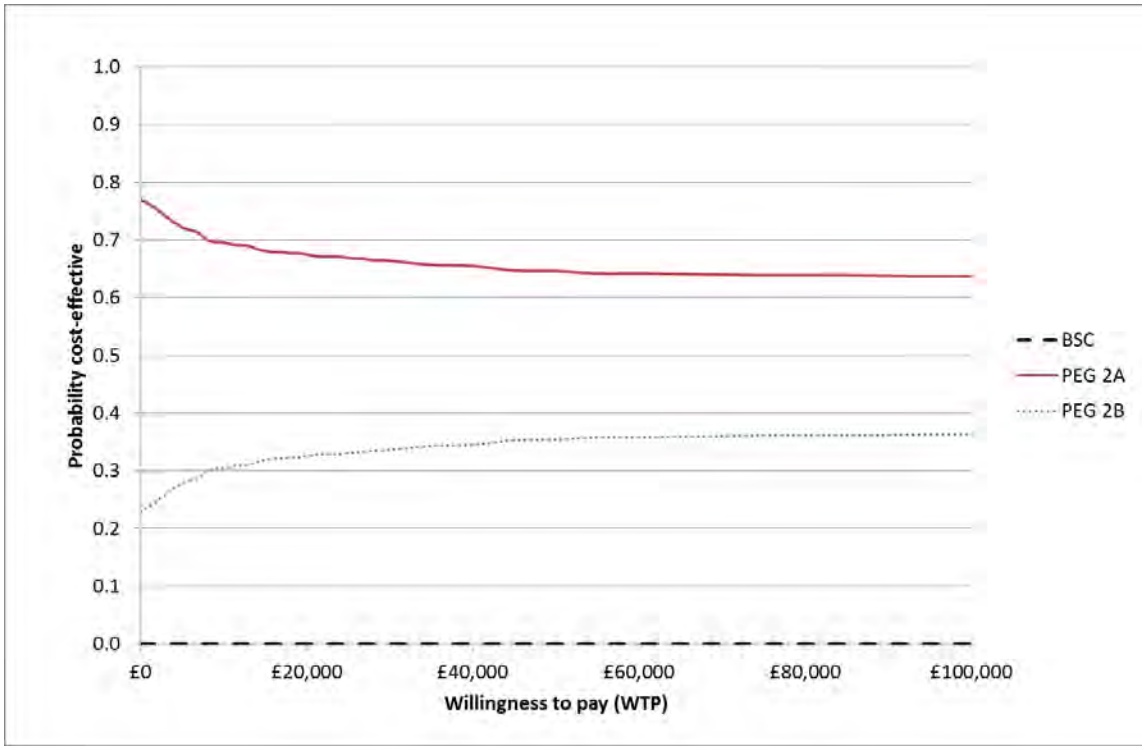


Figure 10 CEAC for the PSA results

Comparison of the cost-effectiveness results from the MS and SHTAC model

The results of the manufacturers' and SHTAC's economic analyses are summarised in Table 47. Roche did not present their results for an all patient cohort, rather they presented their analyses based on genotype groups. The results seen between the three analyses are similar with respect to the overall cost-effectiveness conclusions, that is that peginterferon α-2a and peginterferon α-2b (both in combination with ribavirin) are dominant compared to BSC. MSD and SHTAC also present analyses of the comparison of peginterferon α-2a with peginterferon α-2b as per the NICE scope, and these differ, with MSD suggesting that peginterferon α-2b dominates peginterferon α-2a, whilst SHTAC suggests the opposite, although the difference between the results are marginal.

The total costs vary widely between the analyses, for example the cost of BSC varies between £8,199 (Roche) and £29,245 (SHTAC). Roche uses a much shorter time horizon than the other two analyses which largely explains these differences. The difference in the costs between SHTAC and MSD (for BSC) are due to the length of time patients spend in the HCV health states which is considerably shorter in the SHTAC analysis than for the MSD analysis, and therefore patients incur more health care costs. The incremental costs for peginterferon α-2a versus BSC vary between £3,971 (Roche genotype 1) to -£10,190 (SHTAC).

There is also a wide range in total QALY estimates between the studies. For BSC, these vary between 14.2 years (Roche) to 20.53 (SHTAC). The incremental QALY varies between 1.01 QALYs (Roche

genotype 1) to 2.39 QALYs (MSD). These differences are largely down to the shorter time horizon (Roche) and the lower utility values used in the MSD than in the SHTAC analysis.

Table 47 SHTAC and the manufacturers' baseline cost-effectiveness results

	Analysis	BSC	PEG α 2a	PEG α 2b
Total cost, £	SHTAC	£29,245	£19,055	£20,371
	MSD, all patients	£22,750	£17,798	£17,526
	Roche, genotype 1 + 4	£8,199	£12,170	-
	Roche, genotype 2 + 3	£8,199	£6,336	-
Total QALY	SHTAC	20.53	22.25	22.19
	MSD, all patients	16.77	19.16	19.24
	Roche, genotype 1 + 4	14.20	15.21	-
	Roche, genotype 2 + 3	14.20	15.77	-
Incremental cost vs BSC, £	SHTAC	-	-£10,190	-£8,874
	MSD, all patients	-	-£4,952	-£5,224
	Roche, genotype 1 + 4	-	£3,971	-
	Roche, genotype 2 + 3	-	-£1,864	-
Incremental QALY vs BSC	SHTAC	-	1.72	1.66
	MSD, all patients	-	2.39	2.47
	Roche, genotype 1 + 4	-	1.01	-
	Roche, genotype 2 + 3	-	1.57	-
ICER vs BSC £ per QALY	SHTAC	-	dominates	dominates
	MSD, all patients	-	dominates	dominates
	Roche, genotype 1 + 4	-	£3,915	-
	Roche, genotype 2 + 3	-	dominates	-
ICER PEG α-2b vs PEG α-2a, £ per QALY	SHTAC	-	-	dominated
	MSD, all patients	-	-	dominates
	Roche, genotype 1 + 4	-	-	-
	Roche, genotype 2 + 3	-	-	-

Summary of cost-effectiveness

- A systematic searches of the literature found no studies that met the inclusion criteria. Two cost-effectiveness studies in children were summarised: one abstract and one full economic evaluation for non-pegylated interferon treatment.
- A systematic review of studies of QoL for children with chronic HCV did not identify any relevant studies. An update of searches for QoL for adults found one new study and one previously unidentified study that provided EQ-5D for patients with chronic HCV.
- Two manufacturers submitted evidence to be considered for the appraisal:
    - MSD, the manufacturer of peginterferon α-2b, constructed a lifetime Markov model with a model structure based upon that developed for previous NICE appraisals for adults. The model used the effectiveness of the treatments from a meta-analysis of the clinical trials. The base case results from the submission found that both combinations of peginterferon alfa dominated BSC in all age and genotype subgroups. There were small differences in costs and health outcomes between peginterferon α-2a and peginterferon α-2b. Peginterferon α-2b dominated peginterferon α-2a for most age and genotype subgroups.
    - Roche, the manufacturer of peginterferon α-2a, also constructed a Markov model based upon that developed for previous NICE appraisals for adults, with a time horizon of 30 years. The model used the effectiveness of peginterferon α-2a from a weighted average of the four clinical trials. The base case results from the submission found that peginterferon α-2a is a cost-effective option for the treatment of paediatric HCV compared to BSC for the treatment of genotype 1,4 and 5 patients (ICER of £3,914/QALY gained) and genotype 2 and 3 (ICER dominates).
- The authors of this report developed an independent Markov model, based upon that developed for previous NICE appraisals for adults, with a time horizon of 70 years. From this model, peginterferon alfa in combination with ribavirin was more effective and cheaper than BSC. The costs were slightly lower for peginterferon α-2a compared to peginterferon α-2b and the QALYs slightly higher, thus peginterferon α-2b was dominated by peginterferon α-2a. The deterministic sensitivity analyses showed that these conclusions for peginterferon alfa compared to BSC were robust for all changes to the structural assumptions and input parameters. Peginterferon α-2b dominates peginterferon α-2a for all sensitivity analyses except for changes to the SVR. The model results are most sensitive to changes in the discount rate, time horizon, the treatment SVR and the starting fibrosis make-up of the cohort. According to the PSA, peginterferon α-2a has the greatest probability of being cost-effective at a willingness to pay threshold of £30,000 per QALY.

6 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

Peginterferon α-2a and α-2b in combination with ribavirin are used in the treatment of adults with chronic HCV following previous NICE guidance[32-34] and our expert clinical advisors suggest that many children with chronic HCV are currently treated with peginterferon alfa and ribavirin. The small number of children with chronic HCV in the UK are generally referred to one of the three specialist paediatric hepatology centres, although can be managed within shared care networks at local clinics. If there were to be wider access to treatment, there may be an impact in terms of resources such as recruitment and training of specialist hepatology nurses, and additional input from GP's and child psychology services.

Apart from peginterferon alfa, there are currently no other licensed agents available and hence limited treatment options for this population. Peginterferon alfa and ribavirin treatment may therefore be considered to be novel therapies for children and young people less than 18 years of age who have not previously had access to treatment for chronic HCV. Clinicians are of the opinion that this is a rapidly changing treatment community with other newer drugs in the pipeline which include non-interferon-based therapies such as protease inhibitors (see section 8.2). The emergence of newer treatment options may affect the uptake of peginterferon alfa and ribavirin therapy and consequently, those with less favourable genotypes may prefer to wait for newer drugs.

We are not aware of any issues relating to equality.

7 DISCUSSION

7.1 Statement of principal findings

Clinical effectiveness

The results of seven studies evaluating peginterferon alfa treatment in children and young people were included in this systematic review. The evidence was limited to uncontrolled single cohort studies (with one RCT treated as a single cohort study) which had relatively small populations. Overall the studies were of low methodological quality and, due to the nature of the design, few statistical analyses were reported.

The studies varied in their population characteristics according to a number of factors including HCV genotype mix, mean participant age, treatment history, mode of HCV transmission, baseline HCV RNA levels, and different countries involved. Six studies excluded those co-infected with HIV or hepatitis B, three peginterferon α-2b studies[46;47;52] specifically excluded younger children (<8 years

old), two[48;52] (peginterferon α-2b) included a mix of treatment naïve and previously treated children (with a third study unclear[47]) and only one study[58] (peginterferon α-2a) included UK participants. The design and quality of the studies, as well as other uncertainties, makes assessment of the generalisability of the studies difficult and the variation in these factors may have implications for the interpretation of the findings.

The SVR rates in the included studies ranged from 53-66% in children treated with peginterferon α-2a and 29-75% for those treated with peginterferon α-2b, although the range was 49-65% if two studies with very small participant numbers[46;47] are excluded. These rates are comparable to those seen in adults with chronic HCV (50-60%[20]). Observed patterns in the SVR subgroups (genotype 2 or 3, treatment naïve, low viral load at baseline) also appear to be consistent with what is seen in adults, i.e. higher SVR rates are observed in these subgroups. However, the numbers of children in some of these subgroups were very small and none of the studies was powered for subgroup analysis, therefore results should be interpreted with caution. Serious adverse events were defined differently in the studies and the amount of data provided on adverse events varied considerably from one study to the next. However, overall the relatively mild adverse events typically associated with the use of peginterferon and ribavirin were frequent (e.g. flu-like symptoms were almost universal) and consistent with that in adults.

No studies were identified that directly compared peginterferon α-2a with peginterferon α-2b and any comparison would be by observation of data only so no conclusions can be drawn in the present review. Two recent (2010)[89;90] meta-analyses of RCTs comparing peginterferon α-2a with peginterferon α-2b in adults both concluded that no recommendations could be made of one over the other. It remains inconclusive whether the two peginterferon alfa forms are equally effective in children.

Cost-effectiveness

Systematic searches did not identify any evidence that met the criteria for the systematic review of cost-effectiveness studies of peginterferon alfa treatments in children or HRQoL in children with chronic HCV. A small number of studies with some limited relevance were identified (although not meeting the inclusion criteria) and were summarised for context to the cost-effectiveness analysis.

Two manufacturers submitted evidence for the cost-effectiveness of their respective treatments versus BSC, and one (MSD) also compared the cost-effectiveness of the two treatments. Both manufacturers based their model structure on one previously developed for NICE appraisals of these treatments in adults. There were differences however in the time horizon, and the sources of the effectiveness data. MSD used a lifetime horizon and Roche a 30 year time horizon. Effectiveness data were sourced from

a meta-analysis of single-cohort studies in the MSD model and a weighted average of single-cohort studies in the Roche model. Neither approach was assessed by the present review of clinical effectiveness to be robust, and these estimates should therefore be treated with caution. In the MSD model the base case results found that both combinations of peginterferon alfa dominated BSC in all age and genotype subgroups. There were small differences in costs and health outcomes between peginterferon α-2a and peginterferon α-2b. Peginterferon α-2b dominated peginterferon α-2a for most age and genotype subgroups. In the Roche model the base case results found that peginterferon α-2a is a cost effective option for the treatment of paediatric HCV compared to BSC. Both submissions were assessed to meet the majority of quality standards required of an economic evaluation.

An independent Markov model, based upon the previous SHTAC model, was undertaken by the assessment group to assess the cost-effectiveness of the two peginterferon alfa treatments in combination with ribavirin compared with BSC and one another, as per the NICE scope. A 70 year time horizon was used. Many of the assumptions used previously were employed, with the addition of assumptions that no children would have spontaneous viral clearance, that treatment would discontinue if an EVR was not achieved at week 12, and that adult transition probabilities, utility weights and health state costs were applied for paediatric patients due to lack of data. Effectiveness data were taken from the studies identified in the systematic review of clinical effectiveness where a weighted average approach was used to establish the SVRs and EVRs. Utility data were taken from published sources, although as noted above these were in adult populations. Results from this model, albeit based upon poor evidence, suggest that peginterferon alfa (α-2a or α-2b) in combination with ribavirin was more effective and less expensive than BSC. Peginterferon α-2a is slightly cheaper and more effective compared to peginterferon α-2b in the overall population and the subgroup genotype 1or 4, but not in the subgroup with genotype 2 or 3.

7.2 Strengths and limitations of the assessment

Strengths

The current technology assessment addresses a specific knowledge gap concerning the clinical and cost-effectiveness of peginterferon α-2a and peginterferon α-2b in children and adolescents with chronic hepatitis C.

This technology assessment report has been undertaken by an independent evidence synthesis team free of any vested interest. The technology assessment addressed a clear question with a well-defined specific population, intervention, comparator and outcomes. An independent advisory group including clinical experts commented on the research protocol and the final report. The systematic review of clinical effectiveness followed standard principles of evidence synthesis recommended by the CRD to

minimise bias.[43] The methods were set out *a priori* in a peer-reviewed research protocol that defined the research question, inclusion criteria, critical appraisal approach, data extraction process, and the methods of data synthesis to be used (see Appendix 1). The study selection step was conducted independently by two reviewers and all other steps were conducted by one reviewer and checked independently by a second reviewer, with all decisions recorded and transparently reported.

An economic model has been developed following recognised guidelines,[44;45] and systematic searches have been conducted to identify data for the economic model. The searches, critical appraisal of the economic evidence, and development and reporting of the economic model were conducted by one reviewer and checked independently by a second reviewer.

Manufacturers' submissions of evidence were systematically data-extracted and critically appraised by the review team using a standard health economic evaluation checklist (Appendix 9) and, where appropriate, information from the submissions was used to inform the economic evaluation.

The model captures variability and uncertainty in effectiveness, costs and clinical practice using one-way deterministic sensitivity analysis to evaluate the influence of individual parameters, model structure and assumptions on the robustness of the model. Multi-parameter uncertainty was addressed using probabilistic sensitivity analyses for a range of parameter distributions (Appendix 10), whilst scenario analyses were used to explore differences between the treatments and the effect of varying the rate of progression to cirrhosis. Uncertainty around the cost-effectiveness of the interventions for different willingness-to-pay thresholds is represented transparently in cost-effectiveness acceptability curves.

Limitations

Despite the extensive and systematic searches, relatively little clinical effectiveness evidence was found, with only two studies of peginterferon α-2a and five studies of peginterferon α-2b meeting the inclusion criteria for the systematic review. These were small studies, with only 7-107 participants. Although one study was an RCT, only one of its arms was relevant, meaning that no head-to head comparisons of peginterferon alfa against BSC, or peginterferon α-2a against peginterferon α-2b were available. The available evidence thus relies solely on pre-to-post-intervention comparisons of outcomes within single cohorts of participants. On the whole the studies were poorly reported, with high risk of bias, meaning that their results should be interpreted with caution. Although all studies reported the primary outcome (SVR), some other relevant outcomes were only reported in a few studies, meaning that no conclusions can be drawn regarding the effectiveness of peginterferon α-2a or α-2b on biochemical response (normalisation of ALT levels), histological response (degree of

inflammation, fibrosis or cirrhosis), quality of life, or growth (height or weight changes were reported in most studies but effects were not consistent).

Due to heterogeneity among the studies in their participant characteristics and a lack of information on the variance of SVR estimates, quantitative meta-analysis to obtain pooled effect estimates was not appropriate. The smallest study (which had only seven participants and was not conducted in the UK) was an outlier in having a considerably lower SVR than the six other studies. With such small studies it can be difficult to determine whether they should be classed as a prospective cohort or case series (our inclusion criteria were conservative in order not to exclude potentially relevant evidence). The possible implications of including or excluding this study were considered as part of a structured narrative synthesis.

As noted previously, generalisability of the clinical effectiveness studies is difficult to determine. The generalisability to a UK paediatric population is uncertain and the results may also not be generalisable to participants with hepatic co-morbidities, since the studies excluded participants with hepatitis B and HIV and, in some cases, other liver diseases. There were no studies identified in children and young people with HIV co-infection that met the inclusion criteria.

A systematic review of the literature for cost-effectiveness studies found none that met the inclusion criteria (two cost-effectiveness studies in children were identified but one was reported superficially only in an abstract whilst the other, a full economic evaluation, included interferon rather than peginterferon treatment). A systematic review of studies of QoL for children with chronic HCV did not identify any relevant studies.

Parameters in the model (disease progression, utility and health state costs) have not been derived for the specific patient group in this assessment, i.e. children, since targeted searches undertaken for this review did not identify suitable data, and so parameter values have been taken for the adult population. It is uncertain how applicable these parameter values are. However, it should be noted that, as the model is a lifetime model, these parameter values are relevant during the adult years. There is also some degree of uncertainty over the intervention costs used, which include monitoring and outpatient costs. In the absence of clinical guidelines in children these were based on the previous assessments in adults and uprated to current values. It is possible that the costs for the tertiary referral centres for children differ from the costs of secondary care in adults.

As there were no direct head-to-head comparisons of the interventions, a pragmatic approach was taken in the economic model to use the available SVR evidence through an unadjusted indirect comparison. Caution is recommended in the interpretation of the economic evaluation because, as no

relevant RCTs were available, there is no means by which the similarity of the included studies can be assessed. The clinical effectiveness data for SVR that were included in the economic model are also limited by the small size and number of the primary research studies that met the inclusion criteria for the clinical effectiveness systematic review. Although the analysis approach has inherent risk of bias, the sensitivity and scenario analyses conducted provide an illustration of the likely estimate of the cost-effectiveness. Due to the large number of parameters included in the sensitivity analyses, some parameters (e.g. for health state costs, transition probabilities and utility values) were combined and varied together rather than individually.

A potential limitation to the current evidence synthesis is that the searches for clinical effectiveness and cost-effectiveness data were limited to English language publications. The approach can be justified since the context of the technology assessment is specifically the NHS in England and Wales. However, only one of the identified studies[58] included any participants from the UK.

Uncertainties

Despite efforts to explore uncertainty in the evidence synthesis, some important uncertainties remain. There is uncertainty about the reliability of the relative SVR effect sizes between peginterferon α-2a and peginterferon α-2b, due to the poor quality of the studies and the lack of head-to-head trials. Variance around the estimates in the study samples is illustrated by SVR rates that range from 53-66% in children treated with peginterferon α-2a and 49-65% for those treated with peginterferon α-2b when excluding two studies of peginterferon α-2b which had very small participant numbers (7 and 12 participants[46;47]). Some studies reported SVR rates in relation to prognostic factors (e.g. genotype or previous treatment history). However, these relationships were reported in few studies, and inevitably involved even smaller numbers of participants than were available for the primary outcome, so their reliability is uncertain.

The cost effectiveness of peginterferon α-2a compared to peginterferon α-2b is proportionate to the relative SVR of these treatments. For strategies where SVR for peginterferon α-2a is greater than or the same as peginterferon α-2b, peginterferon α-2a is the optimal treatment and conversely where SVR for peginterferon α-2b is greater than peginterferon α-2a, peginterferon α-2b is the optimal treatment. This demonstrates the extent of the uncertainty in the base case results. The economic evaluation used a number of assumptions which had been discussed with our expert advisory group. We took a conservative approach to the assumption about treatment stopping in those with genotype 1 or 4 at 24 weeks if no EVR was obtained (at 12 weeks) because expert opinion was mixed. Finally with regard to the parameters in the model, in the absence of data the model assumes that the treatment response is the same across all chronic HCV states (F0-F4) however some uncertainty remains about this assumption.

The distribution of participants to the health states used in the model was based on a weighted average of the distribution of the participants in the studies included in the clinical effectiveness systematic review. It is uncertain how generalisable these populations are to the population of children with chronic HCV in the UK, and it is possible that in the economic model participants may be more or less severe than those seen in the UK.

Growth is an important outcome for assessing the effects of peginterferon alfa and ribavirin in children and adolescents with chronic HCV. The results appear to provide a weak indication that height and/or weight increases were reduced by peginterferon α-2b but not peginterferon α-2a but this may not be reliable since only one peginterferon α-2a study reported this outcome and height/weight changes were not universal in the peginterferon α-2b studies.

Another outcome of particular interest in children and adolescents with chronic HCV is QoL. Experience of clinicians who informed the technology assessment suggests that children and adolescents may experience non-trivial QoL decrements associated with the stigma of the disease. However, there are very limited QoL data available for this population and only one of the included studies addressed this outcome, precluding any conclusions to be drawn concerning the possible impact of peginterferon alfa on children and adolescents with chronic HCV. In the economic model HRQoL was taken from studies in adults owing to a lack of data. It remains uncertain whether there is any impact on parent or carer's QoL and this has not been assessed in the cost-effectiveness model for the current assessment.

The scope of the current technology assessment is explicit about the age of the eligible population, namely adolescents aged 3 to 17 years. A number of primary research studies had populations that did not meet these criteria, since they included younger and/or older participants, and were therefore excluded (reasons for exclusion are reported in Appendix 5). It is unclear whether the inclusion of studies whose populations differed only marginally from the specified age range would have made any difference to the results. Although widening the age range might have allowed more evidence to be considered, it is difficult to determine at what point the age limits would become non-relevant to the decision problem. Also, deviation from the *a priori* specified inclusion criteria may increase the risk of selection bias.

8 CONCLUSIONS

Treatment of children and young people with peginterferon (α-2a or α-2b) and ribavirin may be a viable option. Results from the independent Markov model suggest that peginterferon (α-2a or α-2b) in combination with ribavirin is more effective and less expensive than BSC. However, the available evidence is of poor quality.

8.1 Implications for service provision

A recommendation for treatment with peginterferon alfa and ribavirin in children and young people with chronic HCV could potentially cause difficulties with delivery of the service in terms of accessibility. There are currently only three specialised paediatric hepatology centres in the UK that treat children (located in London, Leeds and Birmingham), meaning that the nearest treatment centre could potentially be quite some distance, with resultant implications of time off school and work (for parents). However, our clinical advisors affirm that shared care pathways are well-established in the UK with treatment and overall care delivered outside of the three specialist centres at joint clinics. The challenge for treating children and young people in more centres would be in making treatment accessible to all patients but with each centre treating enough patients to maintain expertise. Other implications of a recommendation for treatment that should be considered are the possible need for more clinical nurse specialists and the additional burden on GP's, haematologists and child psychology services as a result of managing adverse effects.

8.2 Suggested research priorities

The evidence included in this review comes from poor quality uncontrolled cohort studies that are relatively small and have uncertain generalisability to the UK population of children and young people with chronic HCV. Ideally, better quality evidence should come from well-designed RCTs, although there may be ethical issues with randomising children to placebo. Well-conducted, head to head RCTs of peginterferon α-2a and ribavirin versus peginterferon α-2b and ribavirin would provide the best evidence of the effectiveness of these treatments but it is unclear whether these are likely given the emergence of newer treatments. If larger cohort studies were carried out, they should be statistically powered for the various subgroups in whom treatment response varies (e.g. genotype, treatment history, baseline viral load, etc.), and be conducted in participants that reflect the chronic HCV paediatric population in the UK. The adverse effects of peginterferon alfa treatment on growth in children is a concern, as is the impact on HRQoL, but data in the included studies is sparse and is short-term. Longer-term, more robust data are required to ascertain the long-term impact of peginterferon alfa treatment on the growth and quality of life of children and young people with chronic HCV.

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. Davison SM, Mieli-Vergani G, Sira J, Kelly DA. Perinatal hepatitis C virus infection: diagnosis and management. *Arch Dis Child* 2006;**91**:781-85.

5. Wirth S, Kelly D, Sokal E, Socha P, Mieli-Vergani G, Dhawan A *et al*. Guidance for Clinical Trials for Children and Adolescents with Chronic Hepatitis C. *J Pediatr Gastroenterol & Nutr* 2011;**52**:233-7.

6. Robinson JL,.Doucette K. The natural history of hepatitis C virus infection acquired during childhood. *Liver International* 2012;**32**:258-70.

7. Wirth S. Current treatment options and response rates in children with chronic hepatitis C. *World J Gastroenterol* 2012;**18**:99-104.

8. Roy A, Schwarz K. *Hepatitis C in Children*. Hepatitis C Choices, Caring Ambassadors Program, Inc, 2008.

9. Yeung LTF, King SM, Roberts EA. Mother-to-infant transmission of hepatitis C virus. *Hepatology* 2001;**34**:223-9.

10. Health Protection Agency. *Hepatitis C in the UK: 2011 Report*. London: Health Protection Agency; 2011.

11. Hu J, Doucette K, Hartling L, Tjosvold L, Robinson J. Treatment of Hepatitis C in Children: A systematic review. *PLoS ONE* 2010;**5(7)**:e11542.

12. Bortolotti F, Verucchi G, Camma C, Cabibbo G, Zancan L, Indolfi G *et al*. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. *Gastroenterol* 2008;**134**:1900-7.

13. Harris HE, Mieli-Vergani G, Kelly D, Davison S, Gibb DM, Ramsay ME *et al*. A national sample of individuals who acquired hepatitis C virus infections in childhood or adolescence: risk factors for advanced disease. *J Pediatr Gastroenterol & Nutr* 2007;**45**:335-41.

14. Jara P, Resti M, Hierro L, Giacchino R, Barbera C, Zancan L *et al*. Chronic hepatitis C infection in childhood: clinical patterns and evolution in 224 white children. *Clin Infect Dis* 2003;**36**:275-80.

15. Rumbo C, Fawaz RL, Emre SH, Suchy FJ, Kerkar N, Morotti RA *et al*. Hepatitis C in children: a quaternary referral center perspective. *J Pediatr Gastroenterol & Nutr* 2006;**43**:209-16.

16. Mack CL, Gonzalez-Peralta RP, Gupta N, Leung D, Narkewicz MR, Roberts EA *et al*. NASPGHAN practice guidelines: Diagnosis and management of hepatitis C infection in infancts, children and adolescents. *JPGN* 2012;**54**:838-55.

17. Rerksuppaphol S, Hardikar W, Dore GJ. Long-term outcome of vertically acquired and post-transfusion hepatitis C infection in children. *J Gastroenterol & Hepatology* 2004;**19**:1357-62.

18. England K, Thorne C, Harris H, Ramsay M, Newell ML. The impact of mode of acquisition on biological markers of paediatric hepatitis C virus infection. *J Viral Hepatitis* 2011;**18**:533-41.

19. Jhaveri R. Diagnosis and management of hepatitis C virus-infected children. *Pediatr Infect Dis Journal* 2011;**30**:983-85.

20. 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**.

21. 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.

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

23. 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.

24. 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.

25. Akobeng AK, Davison S. Quality of Life of Patients With Chronic Hepatitis C Virus Infection. *J Pediatr Gastroenterol & Nutr* 2000;**30**:224-6.

26. Nydegger A, Srivastava A, Wake M, Smith AL, Hardikar W. Health-related quality of life in children with hepatitis C acquired in the first year of life. *J Gastroenterol & Hepatology* 2008;**23**:226-30.

27. Rodrigue JR, Balistreri W, Haber B, Jonas MM, Mohan P, Molleston JP *et al*. Impact of hepatitis C virus infection on children and their caregivers: quality of life, cognitive, and emotional outcomes. *J Pediatr Gastroenterol & Nutr* 2009;**48**:341-7.

28. Rodrigue JR, Balistreri W, Haber B, Jonas MM, Mohan P, Molleston JP *et al*. Peginterferon with or without ribavirin has minimal effect on quality of life, behavioral/emotional, and cognitive outcomes in children. *Hepatology* 2011;**53**:1468-75.

29. Zacks S, Beavers K, Theodore D, Dougherty K, Batey B, Shumaker J *et al*. Social stigmatization and Hepatitis C virus infection. *J Clin Gastroenterol* 2006;**40**:220-4.

30. Omland LH, Krarup H, Jepsen P, Georgsen J, Harritshøj LH, Riisom K *et al*. Mortality in patients with chronic and cleared hepatitis C viral infection: a nationwide cohort study. *J Hepatology* 2010;**53**:36-42.

31. Jhaveri, R., Grant, W., Kauf, T. L., and McHutchison, J. The burden of hepatitis C virus infection in children: estimated direct medical costs over a 10-year period. *Journal of Pediatrics* 2006;**148**:353-358.

32. National Institute for Health and Clinical Excellence (NICE). *Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C.* Technology Appraisal

Guidance No. 75. London: NICE; 2000. Available at: *http://publications.nice.org.uk/interferon-alfa-pegylated-and-non-pegylated-and-ribavirin-for-the-treatment-of-chronic-hepatitis-ta75/guidance*. Accessed 21-5-0012

33. National Institute for Health and Clinical Excellence (NICE). *Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C.* Technology Appraisal Guidance No. 106. London: NICE; 2006. Available at: *http://publications.nice.org.uk/peginterferon-alfa-and-ribavirin-for-the-treatment-of-mild-chronic-hepatitis-c-ta106*. Accessed 21-5-0012

34. National Institute for Health and Clinical Excellence (NICE). *Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C.* Technology Appraisal Guidance No. 200 (Part Review of TA75 and 106). London: NICE; 2010. Available at: *http://publications.nice.org.uk/peginterferon-alfa-and-ribavirin-for-the-treatment-of-chronic-hepatitis-c-ta200*. Accessed 21-5-0012

35. Scottish Intercollegiate Guidelines Network (SIGN). *Management of hepatitis C. A national clinical guideline.* Edinburgh: SIGN; 2006.

36. Bruno R, Sacchi P, Ciappina V, Zochetti C, Patruno S, Maiocchi L *et al*. Viral dynamics and pharmacokinetics of peginterferon alpha-2a and peginterferon alpha-2b in naive patients with chronic hepatitis c: a randomized, controlled study. *Antiviral Therapy* 2004;**9**:491-7.

37. Roche Products Limited. *Summary of Product Characteristics - Peginterferon alfa-2a (Pegasys).* European Medicines Agency. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000395/human_med_000974.jsp&mid=WC0b01ac058001d124 Accessed 21-5-2012.

38. Merck Sharp and Dohme Limited. *Summary of Product Characteristics - Peginterferon alfa-2b (ViraferonPeg).* European Medicines Agency. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000329/human_med_001142.jsp&mid=WC0b01ac058001d124 Accessed 21-5-2012.

39. Merck Sharp and Dohme Limited. *Summary of Product Characteristics - Ribavirin (Rebetol).* European Medicines Agency. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000246/human_med_001017.jsp&mid=WC0b01ac058001d124 Accessed 21-5-2012.

40. Roche Products Limited. *Summary of Product Characteristics - Ribavirin (Copegus).* Electronic Medicines Compendium. http://www.medicines.org.uk/EMC/medicine/10081/SPC/Pegasys+135mcg+and+180mcg++solution+for+injection+in+Pre-filled+Syringe+Pre-filled+Pen/ Accessed 21-5-2012.

41. Hartwell D, Jones J, Baxter L, Shepherd J. 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. *Health Technol Assess* 2011;**15**.

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

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

44. Drummond MF,.Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;**313**:275-83.

45. 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.

46. Al Ali J, Owayed S, Al-Qabandi W, Husain K, Hasan F. Pegylated interferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C genotype 4 in adolescents. *Annals of Hepatology* 2010;**9**:156-60.

47. Ghaffar TY, El Naghy S, El Sebaie H, El Monaiery M, Ghaffar AY. Pegylated alpha interferon 2B plus ribavirin in the treatment of HCV genotype 4 infection. *Indian J Pediatr* 2009;**76**:895-8.

48. Jara P, Hierro L, de l, V, Diaz C, Camarena C, Frauca E *et al*. Efficacy and safety of peginterferon-alpha2b and ribavirin combination therapy in children with chronic hepatitis C infection. *Pediatr Infect Dis J* 2008;**27**:142-8.

49. Molleston JP, Schwarz KB, Barton BA, Gonzalez-Peralta RP, Narkewicz MR, Haber BA. Autoantibodies and autoimmune disease during the peds-c trial. *J Pediatr Gastroenterol & Nutr* 2009;E73.

50. Murray KF, Rodrigue JR, Gonzalez-Peralta RP, Shepherd J, Barton BA, Robuck PR *et al*. Design of the PEDS-C trial: pegylated interferon +/- ribavirin for children with chronic hepatitis C viral infection. *Clinical Trials* 2007;**4**:661-73.

51. Narkewicz MR, Rosenthal P, Schwarz KB, Drack A, Margolis T, Repka MX *et al*. Ophthalmologic complications in children with chronic hepatitis C treated with pegylated interferon. *J Pediatr Gastroenterol & Nutr* 2010;**51**:183-6.

52. Pawlowska M, Pilarczyk M, Halota W. Virologic response to treatment with Pegylated Interferon alfa-2b and Ribavirin for chronic hepatitis C in children. *Med Sci Mon* 2010;**16**:CR616-CR621.

53. Pawlowska M, Pilarczyk M, Halota W, Jendryczka E. Virological Response to Treatment with Pegylated Interferon Alfa-2B and Ribavirin Chronic Hepatitis C in Children. *Hepatology* 2008;**48**:855A-6A.

54. Rodrigue JR, Balistreri WF, Haber B, Jonas MM, Mohan P, Molleston JP *et al*. Peginterferon alfa-2a with or without ribavirin results in minimal effect on quality of life, emotional, and cognitive outcomes: Results of the Peds-C trial. *Hepatology* 2009;418A.

55. Rosenthal P, Mohan P, Barton B, Robuck PR, Schwarz KB. Incidence of Neutropenia and Impact on Sustained Virological Response (Svr) in Children and Adolescents with Chronic Hepatitis C Treated with Peginterferon with Or Without Ribavirin: the Peds-C Experience. *Hepatology* 2008;**48**:1031A-2A.

56. Schwarz KB, Gonzalez-Peralta RP, Murray KF, Molleston JP, Haber B, Jonas MM *et al*. Peginterferon with Or Without Ribavirin for Chronic Hepatitis C in Children and Adolescents: Final Results of the Peds-C Trial. *Hepatology* 2008;**48**:418A.

57. Schwarz KB, Gonzalez-Peralta RP, Murray KF, Molleston JP, Haber BA, Jonas MM *et al*. The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. *Gastroenterology* 2011;**140**:450-8.

58. Sokal EM, Bourgois A, Stephenne X, Silveira T, Porta G, Gardovska D *et al*. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in children and adolescents. *Journal of Hepatology* 2010;**52**:827-31.

59. Wirth S, Ribes-Koninckx C, Bortolotti F, Zancan L, Jara P, Shelton MM *et al*. Children with HCV Infection Show High Sustained Virologic Response Rates on Peginterferon Alfa-2B Plus Ribavirin Treatment. *Hepatology* 2008;**48**:392A-3A.

60. Wirth S, Ribes-Koninckx C, Calzado MA, Bortolotti F, Zancan L, Jara P *et al*. High sustained virologic response rates in children with chronic hepatitis C receiving peginterferon alfa-2b plus ribavirin. *Journal of Hepatology* 2010;**52**:501-7.

61. National Institute for Health and Clinical Excellence (NICE). Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C in children and young people [ID373]: final scope. NICE . 2012. 2012.

62. Schwarz, K. B. PEDS-C: Pegylated interferon +/- Ribavirin for Children with Hepatitis C. ClinicalTrials.gov study details. Murray et al.{183} . 2011.

63. Jonas MM, Balistreri W, Gonzalez-Peralta RP, Haber B, Lobritto S, Mohan P *et al*. Pegylated interferon for chronic hepatitis C in children affects growth and body composition: results from the pediatric study of hepatitis C (PEDS-C) trial. *Hepatology* 2012;**56**:523-31.

64. Wirth S, Pieper-Boustani H, Lang T, Ballauff A, Kullmer U, Gerner P *et al*. Peginterferon alfa-2b plus ribavirin treatment in children and adolescents with chronic hepatitis C. *Hepatology* 2005;**41**:1013-8.

65. Zhang HF, Yang XJ, Zhu SS, Dong Y, Chen DW, Jia WZ *et al*. An open-label pilot study evaluating the efficacy and safety of peginterferon alfa-2a combined with ribavirin in children with chronic hepatitis C. *Zhonghua Shi Yan He Lin Chuang Bing Du Xue. Za Zhi.* 2005;**19**:185-7.

66. Sluzewski W, Kowala-Piaskowska A, Wysocki J, Figlerowicz M, Gorczyca A, Halota W *et al*. Treatment of chronic hepatitis C in children with pegylated interferon alpha2a and ribavirin--a multi-center study. *Acta Poloniae Pharm* 2012;**69**:319-26.

67. Abdel-Hady MM, Bansal S, Davison S, Brown MP, Tizzard S, Mulla S *et al*. UK experience of treatment of chronic viral hepatitis C in children and adolescents: Predictors of viral response and quality of life. *Hepatology* 2010;780A.

68. Mernagh P, Norris S, Del CM. Anti-viral treatment of chronic hepatitis C in a paediatric population: A cost-effectiveness analysis. *Value in Health* 2011;7.

69. Sinha M,.Das A. Cost-effectivness analysis of different strategies of managment of chronic hepatitis C infection in children. *Pediatr Infect Dis J* 2000;**19**:23-30.

70. National Institute for Health and Clinical Excellence. *Guide to the methods of technology appraisal*. London: NICE; 2008.

71. Bjornsson E, Verbaan H, Oksanen A, Fryden A, Johansson J, Friberg S *et al*. Health-related quality of life in patients with different stages of liver disease induced by hepatitis C. *Scand J Gastroenterol* 2009;**44**:878-87.

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

73. Thompson CJ, Rogers G, Hewson P, Wright D, Anderson R, Cramp M *et al*. Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis. *Health Technol Assess* 2007;**11**:1-206.

74. Curtis, L. Unit Costs of Health and Social Care. http://www.pssru.ac.uk/pdf/uc/uc2010/uc2010.pdf Canterbury: Personal Social Services Research Unit, University of Kent; 2010.

75. Joint Formulary Committee. *British National Formulary No. 61*. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2011.

76. Guido M, Bortolotti F, Leandro G, Jara P, Hierro L, Larrauri J *et al*. Fibrosis in chronic hepatitis C acquired in infancy: is it only a matter of time? *Am J Gastroenterol* 2003;**98**:660-3.

77. Saigal S, Rosenbaum P, Stoskopf B, Hoult L, Furlong W, Feeny D *et al*. Comprehensive assessment of the health status of extremely low birth weight children at eight years of age: comparison with a reference group. *J Pediatr* 1994;**125**:411-7.

78. Ara R,.Brazier J. Populating an economic model with health state utility values: moving towards better practice: *HEDS discussion paper* 2009;**9**.

79. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology* 2008;**48**:418-31.

80. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. 2006.

81. 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.

82. 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.

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

84. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;**35**:1095-108.

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

86. Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D. *CHE Discussion Papers:* 1999;172.

87. Department of Health. NHS reference costs 2010-2011. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_122803. London: Department of Health, UK. Accessed 16-12-2011.

88. Wang Y, Moss J, Thisted R. Predictors of body surface area. *J Clin Anesth* 1992;**4**:4-10.

89. Awad T, Thorlund K, Hauser G, Stimac D, Mabrouk M, Gluud C. Peginterferon alpha-2a is associated with higher sustained virological response than peginterferon alfa-2b in chronic hepatitis C: systematic review of randomized trials. *Hepatology* 2010;**51**:1176-84.

90. Zhao S, Liu E, Chen P, Cheng D, Lu S, Yu Q *et al*. A comparison of peginterferon alfa-2a and alfa-2b for treatment-naive patients with chronic hepatitis C virus: A meta-analysis of randomized trials. *Clin Ther* 2010;**32**:1565-77.

91. Goodman ZD, Makhlouf HR, Liu L, Balistreri W, Gonzalez-Peralta RP, Haber B *et al*. Pathology of chronic hepatitis C in children: liver biopsy findings in the Peds-C Trial. *Hepatology* 2008;**47**:836-43.

92. Cesaro S, Bortolotti F, Petris MG, Brugiolo A, Guido M, Carli M. An updated follow-up of chronic hepatitis C after three decades of observation in pediatric patients cured of malignancy. *Pediatr Blood Cancer* 2010;**55**:108-12.

93. Iorio R, Giannattasio A, Sepe A, Terracciano LM, Vecchione R, Vegnente A. Chronic hepatitis C in childhood: an 18-year experience. *Clin Infect Dis* 2005;**41**:1431-7.

94. Fioredda F, Moser A, Bertoluzzo L, Lackner H, Giacchino R, La SM *et al*. Natural course of HCV infection in childhood cancer survivors. *Support Care Cancer* 2010;**18**:1413-20.

95. Kage M, Fujisawa T, Shiraki K, Tanaka T, Fujisawa T, Kimura A *et al*. Pathology of chronic hepatitis C in children. Child Liver Study Group of Japan. *Hepatology* 1997;**26**:771-5.

96. Barshes NR, Udell IW, Lee TC, O'Mahony CA, Karpen SJ, Carter BA *et al*. The natural history of hepatitis C virus in pediatric liver transplant recipients. *Liver Transp.* 2006;**12**:1119-23.

10 APPENDICES

Appendix 1 Methods from the research protocol
Title of the project

Peginterferon alfa and ribavirin for the treatment of chronic hepatitis C in children and young people.

Report methods for the 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.[43]

Search strategy

A search strategy will be developed and tested by an experienced information scientist. The strategy will be designed to identify all relevant studies investigating the two forms of peginterferon alfa with ribavirin in children with HCV. Separate studies will be conducted to identify studies of clinical effectiveness, cost-effectiveness, health-related quality of life and epidemiology.

The following electronic databases will be searched: The Cochrane Library including the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials, NHS CRD (University of York) - Database of Abstracts of Reviews of Effects (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.

Bibliographies of related papers will be assessed for relevant studies. 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 database inception to the present. For the cost-effectiveness assessment, searches for other evidence to inform cost-effectiveness modelling will be conducted as required and may include a wide range of study types (including non-randomised studies). All searches will be updated when the draft report is under review, prior to submission of the final report.

Inclusion and exclusion criteria

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

Population

Children and young people aged 3 to 17 years (peginterferon alfa-2b), or 5 to 17 years (peginterferon alfa-2a), with chronic hepatitis C, without liver decompensation and who are positive for HCV RNA. All groups will be considered, including:

- People with HIV co-infection
- People with all grades of severity of chronic hepatitis C (mild, moderate and severe)
- People who are treatment naïve or, if appropriate, people who have been previously treated but who relapsed or did not respond.

Interventions

- Peginterferon alfa-2a in combination with ribavirin
- Peginterferon alfa-2b in combination with ribavirin

Comparators

- Best supportive care (e.g. symptomatic treatment, monitoring, treatment without any form of interferon therapy)
- The interventions will be compared with each other within their licensed indications, i.e. peginterferon alfa-2a + ribavirin versus peginterferon alfa-2b + ribavirin

Outcomes

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

- virological response to treatment (e.g. during treatment, end of treatment)
- biochemical response (e.g. ALT)
- liver inflammation and fibrosis
- mortality
- adverse effects of treatment, including effects on growth
- health-related quality of life (HRQoL)

Types of studies

- Randomised controlled trials (RCTs) will be included. Where no RCTs of relevance are identified non-randomised controlled trials will be considered for inclusion. Studies without a control group will only be considered for inclusion in the absence of any controlled studies.
- Studies published in the last five years (i.e. since 2007) as abstracts or conference presentations 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-utility analyses, cost-effectiveness analyses [reporting cost per life year gained], cost-benefit analyses or cost-consequence 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.
- Only studies published in the English language will be included.

Screening and data extraction process

Reference screening

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

Data extraction

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

Quality assessment

The quality of the clinical effectiveness studies will be assessed according to criteria based on that used by the CRD (University of York).[43] 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. Quality assessment of the cost-effectiveness studies is detailed below.

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 and heterogeneity explored. Where data allow, clinical- and cost-effectiveness will be assessed according to HCV genotype.

Report methods for synthesising evidence of cost-effectiveness

Identification and systematic reviewing of published cost-effectiveness studies

The sources outlined above will be used to identify studies of the cost-effectiveness of peginterferon alfa-2a and -2b in combination with ribavirin in children with hepatitis C. The aim of the review is to identify studies that are relevant to the UK NHS. The inclusion and exclusion criteria for the systematic review of published cost-effectiveness studies will be identical to that applied in the systematic review of clinical effectiveness, differing only in study design. The quality of the included economic evaluations will be assessed using a critical appraisal checklist based upon those proposed by Drummond and colleagues[44] and Philips and colleagues.[45] The data from these studies will be tabulated and discussed in a narrative review. 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.

Methods for estimating quality of life

Where presented, HRQoL data will be extracted from studies included in the systematic review of clinical effectiveness, the systematic review of cost-effectiveness or the sponsor submission. In addition, a systematic literature search will be conducted specifically for publications reporting HRQoL or health state utility for children with HCV, including the impact of peginterferon alfa-2a or -2b on these children. Studies will be synthesized through a narrative review with tabulation of results of included studies. Where available, HRQoL data will be used in our economic model. In the absence of evidence that meets our quality criteria, the model may use indirect evidence of quality of life from alternative sources, for example HRQoL from adults with HCV. There are methodological challenges with measuring health state utilities in children, for example the use of parents' valuations as proxies, and these issues will be explored by discussion within the team.

Economic Modelling

The Markov model developed by SHTAC for a previous NICE assessment of treatment for mild chronic hepatitis C[20] will be reviewed to assess its applicability to children within the scope of the

current review. If the model structure is considered appropriate, the model parameters will be further reviewed to determine whether more relevant data are available for disease progression, health state utility or resource use/cost for children with HCV. The perspective for the analysis will be that of the NHS and Personal Social Services, with costs and outcomes discounted at 3.5%. 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 in order to model a lifetime horizon. Incremental cost-effectiveness of the interventions will be estimated in terms of cost per quality-adjusted life year (QALY) gained, as well as the cost per life year gained if data permit.

The simulated population will be defined on the basis of the published evidence about the characteristics of children in the UK with chronic HCV, within the scope of the current review. This will include children with HIV co-infection, or who have been previously treated where good quality clinical effectiveness evidence is available.

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 clinical experts' opinion. Searches for additional information regarding model parameters, patient preferences and other topics will be conducted as required. All updated parameter estimates will be derived from the best available published literature, NHS sources (including the Finance Department at Southampton University Hospitals Trust) and industry submissions, where applicable. Sources for, and methods of, deriving parameter values will be stated clearly.

Adverse effects will be accounted for in the model if these are clearly reported by the trials included in our systematic review of clinical effectiveness. These will be included as an extra cost and, where possible, disutility.

Analysis of uncertainty

Uncertainty will be explored through both one way sensitivity analyses and scenario analysis. A probabilistic sensitivity analysis (PSA) will be undertaken if the both the data and modelling approach permit this. The outputs of any PSA will be presented using plots of the cost–effectiveness plane and cost-effectiveness acceptability curves.

Handling the company submission(s)

All data submitted by the manufacturers will be considered if received by the TAR team no later than 3rd October 2012. 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,[70] 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 for children included in the assessment report together with the results from the Assessment Group's analysis. Reasons for any large discrepancies in estimated ICERs will be explored and, where possible, explained.

Any 'commercial in confidence' data taken from a company submission, and specified as confidential in the check list, will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name, e.g. in brackets).

Appendix 2 Search strategies

Clinical effectiveness searches

The following strategies were used to search MEDLINE (Ovid) and EMBASE (Ovid) from 1946/7 to November 2012. The strategies were translated into the other databases listed in Chapter 3 (*Identification of studies*).

MEDLINE (Ovid)

1 Hepatitis C, Chronic/ (13735)
2 ("hepatitis C" or HCV).tw. (48770)
3 exp Hepatitis C/ (41824)
4 Hepacivirus/ (20518)
5 or/1-4 (56080)
6 Ribavirin/ (7195)
7 (ribavirin* or copegus or rebetol or rebetron or rebretron or ribamide or ribamidil or ribamidyl or ribasphere or varazid or vilona or viramid or virazid or virazole or RibaPak).ti,ab,nm. (9111)
8 6 or 7 (9111)
9 (peginterferon$ or peg-ifn or peg-interferon$ or (pegylat$ adj3 interferon$) or peg$ or (polyethylene glycol adj3 interferon$) or ViraferonPeg or pegintron or "peg-intron" or Pegasys).mp. (29312)
10 Interferon-Alfa/ or Interferons/ (40682)
11 ("IFN alfa" or "IFN alpha" or IFNalfa or IFNalpha or "interferon alfa" or "interferon alpha").tw. (24503)
12 10 or 11 (49805)
13 Polyethylene Glycols/ (32260)
14 12 and 13 (3545)
15 9 or 14 (29368)
16 5 and 8 and 15 (3824)
17 exp Child/ (1432200)
18 Child, Preschool/ (694089)
19 Adolescent/ (1468478)
20 (child* or toddler* or adolesc* or teenage* or youth* or pediatric* or paediatric*).tw. (945660)
21 or/17-20 (2424786)
22 16 and 21 (325)

EMBASE

1 (hepatitis C or hcv).mp. (87019)
2 exp Hepatitis C/ or exp Hepatitis C virus/ (75723)
3 1 or 2 (87019)
4 (peginterferon$ or peg-ifn or peg-interferon$ or (peg$ adj3 interferon$) or (polyethylene glycol adj3 interferon$) or Pegasys or pegintron or viraferonpeg).mp. (13639)
5 peginterferon/ or peginterferon alpha2a/ or peginterferon alpha2b/ (11347)
6 4 or 5 (13639)
7 ribavirin/ (20451)
8 (ribavirin* or copegus or rebetol or rebetron or rebretron or ribamide or ribamidil or ribamidyl or ribasphere or varazid or vilona or viramid or virazid or virazole or RibaPak).ti,ab,tn. (12251)
9 7 or 8 (21598)
10 3 and 6 and 9 (9778)
11 peginterferon alpha2a plus ribavirin/ or peginterferon alpha2b plus ribavirin/ (195)
12 3 and 11 (186)

13 10 or 12 (9809)
14 child/ (1305129)
15 preschool child/ (472983)
16 adolescent/ (1188986)
17 (child$ or toddler$ or adolesc* or teenage* or youth* or pediatric* or paediatric*).tw. (1347475)
18 (preschool* or "pre-school*").tw. (24127)
19 or/14-18 (2545759)
20 13 and 19 (421)
21 limit 13 to (preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) (210)
22 20 or 21 (422)

Cost-effectiveness searches

The following strategies were used to search MEDLINE (Ovid) and EMBASE (Ovid) from 1946/7 to November 2012. The strategies were translated into the other databases listed in Chapter 3 (*Identification of studies*).

MEDLINE

1 Hepatitis C, Chronic/ (13814)
2 ("hepatitis C" or HCV).tw. (48925)
3 exp Hepatitis C/ (41962)
4 Hepacivirus/ (20593)
5 or/1-4 (56255)
6 Ribavirin/ (7252)
7 (ribavirin* or copegus or rebetol or rebetron or rebretron or ribamide or ribamidil or ribamidyl or ribasphere or varazid or vilona or viramid or virazid or virazole or RibaPak).ti,ab,nm. (9176)
8 6 or 7 (9176)
9 (peginterferon$ or peg-ifn or peg-interferon$ or (pegylat$ adj3 interferon$) or peg$ or (polyethylene glycol adj3 interferon$) or ViraferonPeg or pegintron or "peg-intron" or Pegasys).mp. (29508)
10 Interferon-Alfa/ or Interferons/ (40773)
11 ("IFN alfa" or "IFN alpha" or IFNalfa or IFNalpha or "interferon alfa" or "interferon alpha").tw. (24561)
12 10 or 11 (49919)
13 Polyethylene Glycols/ (32457)
14 12 and 13 (3591)
15 9 or 14 (29565)
16 5 and 8 and 15 (3879)
17 exp economics/ (456096)
18 exp economics hospital/ (17917)
19 exp economics pharmaceutical/ (2332)
20 exp economics nursing/ (3862)
21 exp economics medical/ (13273)
22 exp "Costs and Cost Analysis"/ (164677)
23 exp Cost Benefit Analysis/ (53972)
24 exp models economic/ (8599)
25 (cost* adj2 (effective* or benefit* or utilit* or minim*)).tw. (73771)
26 markov chains/ or monte carlo method/ (23357)
27 (decision adj1 (tree* or analys* or model*)).tw. (6891)
28 exp health care costs/ (40596)
29 or/17-28 (520897)

30 16 and 29 (144)
31 (letter or editorial or comment or historical article).pt. (1397929)
32 30 not 31 (141)

EMBASE

1 (hepatitis C or hcv).mp. (88182)
2 exp Hepatitis C/ or exp Hepatitis C virus/ (76553)
3 1 or 2 (88182)
4 (peginterferon$ or peg-ifn or peg-interferon$ or (peg$ adj3 interferon$) or (polyethylene glycol adj3 interferon$) or Pegasys or pegintron or viraferonpeg).mp. (13980)
5 peginterferon/ or peginterferon alpha2a/ or peginterferon alpha2b/ (11579)
6 4 or 5 (13980)
7 ribavirin/ (20743)
8 (ribavirin* or copegus or rebetol or rebetron or rebretron or ribamide or ribamidil or ribamidyl or ribasphere or varazid or vilona or viramid or virazid or virazole or RibaPak).ti,ab,tn. (12561)
9 7 or 8 (21934)
10 3 and 6 and 9 (10038)
11 peginterferon alpha2a plus ribavirin/ or peginterferon alpha2b plus ribavirin/ (203)
12 3 and 11 (194)
13 10 or 12 (10071)
14 *Health Economics/ (16281)
15 *Economics/ (11217)
16 monte carlo method/ (17113)
17 (cost* or economic*).ti. (126413)
18 markov.tw. (11647)
19 "monte carlo".tw. (22996)
20 (cost* adj2 (effective* or utili* or benefit* or minimi* or consequence* or analys* or saving* or breakdown* or estimate* or variable* or allocation* or control* or illness)).tw. (130225)
21 (econom* or pharmacoeconomic* or "pharmaco economic*" or budget*).tw. (214740)
22 cost/ (49867)
23 cost minimization analysis/ (2073)
24 cost of illness/ (12986)
25 cost utility analysis/ (4167)
26 drug cost/ (51793)
27 health care cost/ (110482)
28 economic evaluation/ (7191)
29 pharmacoeconomics/ (5675)
30 budget/ (17530)
31 "resource use".tw. (5040)
32 "resource utili".tw. (1)
33 (decision adj1 (tree* or analys* or model*)).tw. (9480)
34 ("unit cost*" or "hospital cost*" or "health care cost*" or "healthcare cost*" or "medical cost*").tw. (27557)
35 (managed adj2 (care or clinical or network)).tw. (19055)
36 (resource* adj1 allocat*).tw. (5901)
37 (resource* adj1 utili*).tw. (6341)
38 or/14-37 (594150)
39 13 and 38 (533)
40 (cost and effective* and "hepatitis C").ti. (175)
41 (cost and effective* and "hepatitis C").ab. (608)
42 40 or 41 (646)
43 6 and 9 and 42 (208)
44 11 and 42 (4)
45 39 or 43 or 44 (543)

46 (comment or editorial or letter).pt. (1197206)
47 45 not 46 (507)

Health-related quality of life searches

The following strategies were used to search MEDLINE (Ovid) and EMBASE (Ovid) from 1947 to November 2012. The strategies were translated into the other databases listed in Chapter 3 (*Identification of studies*).

MEDLINE

1 value of life/ (5222)
2 quality adjusted life year/ (5699)
3 quality adjusted life.ti,ab. (4572)
4 (qaly$ or qald$ or qale$ or qtime$).ti,ab. (3826)
5 disability adjusted life.ti,ab. (873)
6 daly$.ti,ab. (885)
7 health status indicators/ (17959)
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. (12492)
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. (898)
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. (1941)
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. (18)
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. (303)
13 (euroqol or euro qol or eq5d or eq 5d).ti,ab. (2707)
14 (hql or hqol or h qol or hrqol or hr qol).ti,ab. (5603)
15 (hye or hyes).ti,ab. (52)
16 health$ year$ equivalent$.ti,ab. (36)
17 health utilit$.ab. (770)
18 (hui or hui1 or hui2 or hui3).ti,ab. (700)
19 disutil$.ti,ab. (169)
20 rosser.ti,ab. (72)
21 quality of well being.ti,ab. (297)
22 quality of wellbeing.ti,ab. (5)
23 qwb.ti,ab. (150)
24 willingness to pay.ti,ab. (1664)
25 standard gamble$.ti,ab. (580)
26 time trade off.ti,ab. (604)
27 time tradeoff.ti,ab. (191)
28 tto.ti,ab. (459)
29 (index adj2 well being).mp. (419)
30 (quality adj2 well being).mp. (736)
31 (health adj3 utilit$ ind$).mp. (531)
32 ((multiattribute$ or multi attribute$) adj3 (health ind$ or theor$ or health state$ or utilit$ or analys$)).mp. (206)
33 quality adjusted life year$.mp. (7493)
34 (15D or 15 dimension$).mp. (1018)
35 (12D or 12 dimension$).mp. (314)

36 rating scale$.mp. (74498)
37 linear scal$.mp. (480)
38 linear analog$.mp. (784)
39 visual analog$.mp. (24844)
40 (categor$ adj2 scal$).mp. (1040)
41 or/1-40 (150176)
42 (letter or editorial or comment).pt. (1134806)
43 41 not 42 (146086)
44 Hepatitis C, Chronic/ (13926)
45 ("hepatitis C" or HCV).tw. (49230)
46 exp Hepatitis C/ (42205)
47 Hepacivirus/ (20742)
48 or/44-47 (56582)
49 43 and 48 (441)

EMBASE

1 quality adjusted life year/ (9303)
2 quality adjusted life.ti,ab. (6565)
3 (qaly$ or qald$ or qale$ or qtime$).ti,ab. (6358)
4 disability adjusted life.ti,ab. (1139)
5 daly*.ti,ab. (1265)
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. (17835)
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. (1404)
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. (2980)
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. (31)
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. (376)
11 (euroqol or "euro qol" or "eq5d" or "eq 5d").ti,ab. (4495)
12 (hql or hqol or "h qol" or hrqol or "hr qol").ti,ab. (8357)
13 ("hye" or "hyes").ti,ab. (63)
14 health* year* equivalent*.ti,ab. (41)
15 health utilit*.ti,ab. (1192)
16 (hui or hui1 or hui2 or hui3).ti,ab. (969)
17 disutil*.ti,ab. (270)
18 rosser.ti,ab. (83)
19 quality of well being.ti,ab. (332)
20 quality of wellbeing.ti,ab. (18)
21 qwb.ti,ab. (170)
22 willingness to pay.ti,ab. (2513)
23 standard gamble*.ti,ab. (695)
24 time trade off.ti,ab. (804)
25 time tradeoff.ti,ab. (208)
26 tto.ti,ab. (698)
27 (index adj2 well being).mp. (568)
28 (quality adj2 well being).mp. (994)
29 (health adj3 util* adj ind*).mp. (888)
30 ((multiattribute* or multi attribute*) adj3 (health ind* or theor* or health state* or util* or analys*)).mp. (299)
31 quality adjusted life year*.mp. (11067)

32 health status indicator*.ti,ab. (327)
33 (15D or 15 dimension*).mp. (1511)
34 (12D or 12 dimension*).mp. (452)
35 "health related quality of living".ti,ab. (3)
36 "health related quality of life".ti,ab. (22371)
37 rating scale*.mp. (115178)
38 visual analog*.mp. (42178)
39 (categor* adj scale*).mp. (702)
40 linear scal*.mp. (655)
41 linear analog*.mp. (962)
42 "quality of life".ti. (44803)
43 or/1-42 (231142)
44 (letter or editorial or comment).pt. (1199398)
45 43 not 44 (224733)
46 ("hepatitis C" or HCV).tw. (70769)
47 Hepatitis C/ or Hepatitis C virus/ (76817)
48 hepacivirus.tw. (58)
49 or/46-48 (87733)
50 45 and 49 (942)

Appendix 3 Inclusion criteria worksheet for systematic review of clinical effectiveness

Full paper inclusion coding

Author: *Ref ID:* *Reviewer 1:* *Reviewer 2:*

	Yes	No	Unclear
Population			
Children and young people with chronic hepatitis C (aged 3-17 years)			
Compensated liver disease[a]			
Treatment naïve			
Previously treated			
Mixed treatment (treatment naïve and previously treated)			
Co-infection with HIV			
Mixed age population (i.e. ≤17yrs and ≥18yrs)			
Intervention[b]			
Either:			
Peginterferon alfa-2a + ribavirin			
Peginterferon alfa-2b + ribavirin			
Outcomes			
Sustained virological response (SVR)			
Can also include any of the following outcomes:			
Virological response (e.g. during treatment [RVR, EVR], end of treatment [EOT])			
Biochemical response (e.g. % response, ALT levels)			
Histological response (e.g. % response, liver inflammation and fibrosis)			
Adverse effects (including effects on growth)			
Mortality			
QoL			
Other			
Study design			
Randomised controlled trial (RCT)			
Non-randomised controlled trial (CCT)			
Cohort study - 2 groups			
Cohort study - single arm			
Systematic review			
Other (specify)			
Publication type			
Full text paper			
Conference abstract (published 2007 to 2012 only)			
If the study is an abstract only, is there sufficient detail to be included?			
Comparators[b]			
Either:			
Peginterferon alfa-2a + ribavirin			
Peginterferon alfa-2b + ribavirin			
Best supportive care (symptomatic treatment, monitoring, etc)			
Placebo			
N/A or no comparator			
Other (specify)			
	Include	**Exclude**	**Unclear**
Reviewer 1 Decision			
Reviewer 2 Decision			
Final decision			

[a]Exclude decompensated liver disease / post-transplant;

[b]Exclude PEG monotherapy as an intervention or comparator as not licensed

N.B. **Bold** indicates necessary for inclusion - complete these first. Other items are for information purposes and all should be completed if not an immediate exclude.

Appendix 4 Data extraction forms and critical appraisal

Studies of peginterferon α-2a: Schwarz and colleagues (2011)[57]

Reference and Design	Intervention	Participants	Outcome measures
Ref ID: #54 + related publications #40, 544, 843, 837, 554, 183, 80; also study details on clinicaltrials.gov website #1051 **Author:** Schwarz *et al*.[57] + linked studies[28;49-51;54-56;62] **Year:** 2011 (linked studies 2007-2011) **Study design**: RCT but treated as single cohort **Number of centres:** 11 **Country**: USA **Funding**: Supported by the National Institute of Diabetes and Digestive	**Group 1:** **Drug 1:** PEG α-2a *Dose*: 180µg/1.73m^2 body surface area/wk subcutaneously (max 180µg) *Duration*: 48 weeks **Drug 2:** RBV *Dose*: 15 mg/kg twice daily taken orally (max 1200mg/d if ≥75kg and 1,000mg if <75 kg) *Duration*: 48 weeks **Study design details:** Multi-centre RCT (N=114) but data taken from one arm only as the comparator (PEG + placebo, i.e. PEG monotherapy) is outside the NICE scope. Patients with detectable HCV RNA at 24 weeks were considered treatment failures; PEG + placebo treatment failures were offered open-label PEG + RBV for a further 48 weeks (unless HCV RNA remained positive). Dose reductions were made at 3 levels (for Peg α-2a) and reduced by half (for RBV) according to the extent of specific adverse events. Details reported in	**Total numbers involved**: n=55 PEG+RBV **Treatment naïve:** 100% [62] **Previous treatment:** n/a **HCV/HIV co-infection:** no [62] **Duration of infection, mean (±SD):** 105 months ± 56 **Inclusion criteria**: Aged 5-18 years; chronic HCV infection documented by the presence of HCV RNA in plasma on 2 tests at least 6 months apart; chronic liver disease, as indicated by inflammation and/or fibrosis, consistent with chronic HCV infection on a liver biopsy obtained within the past 36 months, not consistent with other known liver disease and not normal; compensated liver disease (Child-Pugh Grade A); haemoglobin values >11 g/dL for females; >12 g/dL for males; normal thyroid stimulating hormone (TSH); able to swallow a RBV/placebo tablet; signed informed consent from parent/legal guardian and willingness of parent/legal guardian to abide by the requirements of the study. [62] **Exclusion criteria:** Any prior treatment with IFN or RBV; receipt of any investigational drug or any systemic antiviral therapy <6 wks prior to the first dose of study drug (except for patients who have taken or are expected to require acyclovir for herpetic lesions); positive test at screening for anti-HAV IgM Ab, HBsAg, anti-HBc IgM Ab, or anti-HIV Ab; history or other evidence of bleeding from esophageal varices or of a medical condition associated with chronic liver disease other than HCV; decompensated liver disease; history of autoimmune or immunologically mediated disease; absolute neutrophil count <1500 cells/mm^3 , Hb <11 g/dL for females and <12 g/dL for males, WBC>17.5 x 10^9/L, or platelet count <90,000/mm^3; serum creatinine level >1.5 x upper limit of normal for age; major depression or a history of severe psychiatric disorder; chronic pulmonary or cardiac disease associated with functional limitation;	**Primary outcomes**: SVR **Secondary outcomes**: RVR, EVR, ETR; relapse; safety (adverse events) and adherence, durability of response (at years 1 & 2), predictors of SVR; QoL, behavioural/ emotional & cognitive functioning[28;54]; autoantibodies & autoimmune disease[49] (not data extracted); ophthalmologic effects[51] (not data extracted). Also states body composition & growth were measured. **Length of follow up**: 24 wks after treatment cessation; longer-term follow up at 1 and 2 years **Methods of assessing outcomes:** Qualitative HCV RNA assessed with Cobas Amplicor HCV v2.0 (Roche) qualitative PCR with lower limit of detection of 60 IU/mL at baseline and wks 24, 48 & 72. Quantitative HCV RNA assays performed at end of study on plasma stored at -80°C & thawed once. HCV RNA levels measured at entry & wks 1, 3, 5, 12, 24, 48 & 72 using high throughput quantitative assay (Cobas TaqMan HCV Test v2.0 with

and Kidney Diseases; the Food and Drug Administration and in part by the National Institutes of Health/ National Centre for Research Resources. Additional support was provided by Hoffman-La Roche.	supplementary tables.	thyroid disease poorly controlled on prescribed medications; poorly controlled diabetes as defined by HbA1c of > 8%; solid organ or bone marrow transplantation; coagulopathy (INR>1.5); active or suspected cancer or a history of malignancy where the risk of recurrence is >20% within 2 years; haemoglobinopathy; haemophilia; severe retinopathy; severe illness or any other conditions which would make the patient unsuitable for the study; sexually active females of child-bearing potential (defined as age ≥ 10 years) and sexually active men who are not practicing two forms of effective contraception during treatment and during the 6 months after treatment has stopped; pregnancy or breast-feeding; males whose female partners are pregnant; active substance abuse; a sibling and/or any other child living in the same household or sharing the same primary caregiver enrolled in the study. [62] **Age (yrs), mean (±SD)**: 10.7 ± 3.3 5-11yrs: 30/55 (55%) 12-17yrs: 25/55 (46%) **Gender male, n (%)**: 27/55 (49%) **BMI z-scores, mean (±SD)**: 0.8 ± 1.0 **Ethnic groups, n (%)**: non-white: 12/55 (22%) Caucasian: 43/55 (78%)[56] **Mode of infection, n (%)**: Maternal-infant: 39/55 (71%) Transfusion: 6/55 (11%) Other (not specified): 10/55 (18%) (*19% reported in paper*) **Genotypes, n (%)**: 1: 45/55 (82%) 2: 4/55 (7%) 3: 6/55 (11%) 4: not reported 6: 0 **Total Childhood Depression Index raw score, mean (±SD)**: 5.9 ± 4.2 **Sample attrition/dropout**: No losses to follow-up (wk 72) but therapy discontinued in 4 patients (reasons given). 7 (13%) lost to	High Pure System for Viral Nucleic Acid Extraction (Roche Molecular Systems, Pleasanton, CA) with lower limit of quantification of 25 IU/mL and lower limit of detection of 10 IU/mL in EDTA plasma. HCV viral genotyping performed at entry using a line probe assay (Innogenetics, Ghent, Belgium). SVR defined as undetectable plasma HCV RNA (<10 IU/mL) at least 24 wks after treatment cessation (states <100 IU/mL in 2 linked papers[55;56]). RVR defined as lack of detectable plasma HCV RNA at wk 5. EVR defined as a decrease ≥2 $\log_{10}$ IU/mL at wk 12 compared to baseline ETR response defined as no detectable plasma HCV RNA at the end of therapy. Relapse defined as patients with an ETR response who became HCV RNA positive after stopping therapy. Paediatric AIDS Toxicity Table used as a guide for grading severity of adverse events. Medication compliance assessed by coordinators' review of a medication diary completed by parents/guardians, and pill & vial counts by researchers or investigational pharmacists.

		follow-up by the 1st annual visit rising to 10 (18%) by the 2nd annual visit.	Knodell[91] Histological Activity Index and Ishak classification systems used for measurement of fibrosis and inflammation. Measures of QoL, behavioural/emotional & cognitive functioning obtained at baseline and at 24 & 48wks, 6 months post-treatment and at 2 subsequent annual visits. QoL assessed using the CHQ Parent Form 50; the CBCL assessed behavioural functioning; the CDI assessed symptoms of depression; the BRIEF measured cognitive functioning. The CHQ, CBCL & BRIEF were completed by parents, CDI completed by child.[28]

Definitions: BRIEF, Behaviour Rating Inventory of Executive Function; CHQ, Child Health Questionnaire; CBCL, Child Behaviour Checklist; CDI, Children's Depression Inventory; ETR, end of treatment virological response; EVR, early virological response; PCR, polymerase chain reaction; QoL, quality of life; RVR, rapid virological response; SVR, sustained virological response; wk, week.

Participant characteristics /outcomes	**Baseline**	**Post-treatment**	
HCV RNA (log_{10} IU/mL), mean (±SD)	6.2 ± 0.8	1.4 [a]	
HCV RNA ≥600,000 IU/mL, % (n/N)	32/55 (58%)[b]	Not reported	
ALT (IU/L), mean (±SD)	49 ± 59	Not reported	
ALT > upper limit of normal, % (n/N)	32/55 (58%)	Not reported	
AST (U/L), mean (±SD)	45 ± 40	Not reported	
AST > upper limit of normal, % (n/N)	28/55 (51%)	Not reported	
Histological Activity Index (inflammation), % (n/N) Minimal (1-3) Mild (4-6) Moderate (7-9) Marked (10-12)	 23/54 (43%) 10/54 (19%) 19/54 (35%) 2/54 (4%)	Not reported	
Steatosis, % (n/N) None Minimal (≤5% of tissue) Mild (6-33%)	 29/54 (54%) 21/54 (39%) 4/54 (7%)	Not reported	

Fibrosis score, % (n/N) None Portal-periportal fibrosis (Ishak 1-2) Bridging fibrosis (Ishak 3-4) Cirrhosis (Ishak 5-6)	 7/54 (13%) 43/54 (80%) 4/54 (7%) 0	Not reported	
Notes/comments: ALT, alanine aminotransferase; AST, aspartate aminotransferase. Results for ALT, AST and HCV RNA are geometric mean ± SD. [a]Mean HCV RNA $\log_{10}$ levels decreased from baseline but data was reported in a line graph so value (at 24 weeks) estimated by reviewer; [b]paper states 70%.			
Outcomes	**Baseline**	**Post-treatment**	**p-value**
Viral Response, n/N (%, 95% CI) RVR (wk 5)	 n/a	 13/55[c] (24%)	 n/a
EVR (wk 12)	n/a	32/55[c] (59%)	n/a
Virological response at wk 24	n/a	41/55[c] (75%)	n/a
ETR (wk 48)	n/a	35/55[c] (64%) [d]	n/a
SVR (wk 72)	n/a	29/55 (53%, 40-66%)	n/a
Notes/comments: [c]n calculated by reviewer; [d]reports 65% in text.			
SVR according to baseline characteristics, n/N (%, 95% CI): HCV RNA <600,000 IU/mL	 n/a	 16/23 (70%)	 n/a
HCV RNA ≥600,000 IU/mL	n/a	16/32 (50%)	n/a
Normal ALT	n/a	16/23 (70%, 51-88%)	n/a
ALT > upper limit of normal	n/a	13/32 (41%, 24-58%)	n/a
Genotype 1	n/a	21/45 (47%, 32-61%)	n/a
Genotype 2-6	n/a	8/10 (80%, 55-100%)	n/a
Inflammation HAI: Minimal (1-3) Mild-Marked (4-12)	n/a	 10/23 (43%, 23-64%) 18/31 (58%, 41-75%)	n/a
Fibrosis stage: None Stage 1-6	n/a	 3/7 (43%, 6-80%) 25/47 (53%, 39-67%)	n/a
Steatosis: Present Absent	n/a	 9/25 (36%, 17-55%) 19/29 (66%, 48-83%)	n/a
Non-response, % (n/N):	n/a	14/55 (25%)[28]	n/a
Relapse, % (n/N):	n/a	17% (9/55) [c]	n/a
Notes/comments: [c]n calculated by reviewer. • SVR according to age, gender and ethnicity also reported but data not extracted here. • In post-hoc multivariate analysis, significant predictors of SVR were treatment with PEG+RBV (OR 4.5, p=0.13), female sex (OR 4.5, p=0.03), non-maternal route of HCV transmission (OR 6.9, p=0.02), genotype non-1 (OR 6.1, p=0.02), moderate or marked inflammation on liver histology (OR 4.2, p=0.04), absence of steatosis (OR 3.9, p=0.04) and lower baseline HCV RNA levels (OR 5.5, p=0.0008). • Patterns of viral response during the first 12 weeks as predictors of SVR in children with genotype 1 were also reported, but data has not been extracted here. • For those children who achieved an SVR who were followed up for 2 years (45/55, 82%), durability of viral response was 100%.			
Quality of life outcomes at 24 wks (n=55), mean ± SD:[28] CHQ Physical summary[e,f]	 52.1 ± 4.8	 49.8 ± 7.5	Mean change 2.40 ± 6.8, p=0.013 [54]
CHQ Psychosocial summary	52.1 ± 7.9	52.3 ± 10.2	
CBCL Internalising[g]	52.4 ± 8.5	51.0 ± 11.0	p=ns[54]
CBCL Externalising[g]	50.4 ± 9.4	48.8 ± 10.3	p=ns[54]
CBCL Total Behaviour Problem[g]	51.5 ± 9.3	49.7 ± 10.2	p=ns[54]
CDI Total score[g]	5.9 ± 4.2	6.2 ± 5.6	p=ns[54]

BRIEF Global Executive Composite[g]	53.5 ± 9.9		52.2 ± 10.1	p=ns[54]
Change in Quality of life at 24 weeks, n/N (%):[28]	**Clinically significant improvement**		**Clinically significant decline**	**No clinical change**
CHQ Physical summary	0		8/55 (15%)	47/55 (86%)
CHQ Psychosocial summary	3/55 (5%)		4/55 (7%)	48/55 (88%)
CBCL Internalising	2/55 (4%)		3/55 (5%)	50/55 (91%)
CBCL Externalising	1/55 (2%)		3/55 (5%)	51/55 (93%)
CBCL Total Behaviour Problem	1/55 (2%)		2/55 (4%)	52/55 (95%)
CDI Total score	0		3/55 (5%)	52/55 (95%)
BRIEF Global Executive Composite	3/55 (5%)		3/55 (5%)	49/55 (90%)
Quality of life for those with virological response at 24 weeks, (n=41), mean ± SD:[28]	**Baseline**	**24 weeks**	**48 weeks**	**6 months**
CHQ Physical summary[h]	52.5 ± 4.2	49.3 ± 7.6	50.7 ± 8.0	51.9 ± 7.5
CHQ Psychosocial summary[h]	52.3 ± 8.1	52.0 ± 9.3	51.9 ± 8.4	52.9 ± 9.3
CBCL Internalising[h]	53.9 ± 8.4	50.9 ± 11.3	49.7 ± 10.4	49.1 ± 10.8
CBCL Externalising[h]	51.9 ± 9.0	49.9 ± 9.9	49.4 ± 9.5	48.5 ± 10.5
CBCL Total Behaviour Problem[h]	52.8 ± 8.5	50.4 ± 10.1	50.0 ± 10.3	48.5 ± 11.9
CDI Total score[h]	6.2 ±4.4	6.1 ± 5.0	5.7 ± 3.8	4.7 ± 3.3
BRIEF Global Executive Composite[h]	53.1 ± 10.5	52.5 ± 9.7	52.4 ± 12.1	51.8 ± 11.1
Adverse Events, % (n/N)				
Dose discontinuation	n/a		7% (4/55)[i,j]	
Dose reduction: PEG RBV	n/a		51% (28/55)[c56] 38% (21/55)[c] 25% (14/55)[c]	
Dose reduction for anaemia	n/a		11% (6/55)[55]	
Dose reduction for thrombocytopenia	n/a		2% (1/55)[55]	
Specific adverse events, % (n/N):				
Flu-like symptoms	n/a		50/55 (91%)	
Headache	n/a		34/55 (62%)	
Gastrointestinal symptoms	n/a		31/55 (56%)	
Injection site reactions	n/a		25/55 (45%)	
Joint/muscle aches	n/a		20/55 (36%)	
Irritability	n/a		17/55 (31%)	
Fatigue	n/a		15/55 (27%)	
Rash	n/a		11/55 (20%)	
Itching	n/a		8/55 (15%)	
Anorexia	n/a		7/55 (13%)	
Trouble sleeping	n/a		6/55 (11%)	
Depression	n/a		2/55 (4%)	
Mortality, % (n/N)	n/a		Not reported	
Effects on growth	n/a		Not reported[k]	

Notes/comments: ns, not statistically significant.

- [c]n calculated by reviewer.
- [e]After 24 weeks of treatment, mean physical QoL scores declined significantly for both groups (PEG+RBV and PEG+Placebo) from baseline (F = 5.8, p=0.004), although scores remained in the average range.
- [f]Individual CHQ analysis showed a statistically significant worsening of bodily pain and general health scores from baseline to 24 weeks (data not reported separately for PEG+RBV group).
- [g]There were no statistically significant time effects (changes from baseline to week 24) for behavioural/ emotional or cognitive functioning (p>0.05).[28;54]
- [h]Repeated measures ANOVA showed that there were no statistically significant time effects for any of the outcome measures during the 48 weeks of treatment or at the 6 month follow-up assessment (p>0.05).[28] However, Rodrigue abstract[54] reports that at week 48, children in the PEG+RBV group had significantly

fewer internalising (mean change 4.06 ± 9.4, p=0.02) and total behaviour problems (mean change 3.38 ± 8.1, p=0.025) relative to baseline scores.

- Among the 41 children who continued PEG+RBV treatment for 48 weeks:[28]
  - 34/41 (83%) experienced no clinically significant change on physical QoL during treatment
  - 2/41 (5%) experienced a clinical decline in physical QoL at 24 weeks but returned to baseline levels by the end of treatment
  - 5/41 (12%) experienced an early clinical decline that persisted to the end of treatment (though 3 of these 5 returned to baseline QoL levels by the 6 month follow up.
  - Most children experienced no clinically significant change in internalising behaviours (95%), externalising behaviours (95%) or total behaviour problems (93%).
  - 2/41 (5%) had a clinically significant increase in depression symptoms (CDI) during treatment – 1 was removed from the study (suicide gesture patient reported in attrition), the other's symptoms remitted by the end of treatment.
  - 1/41 experienced a clinically significant decline in executive functioning at 24 weeks which persisted through treatment and the 6 month follow-up.
- For all children who completed 48 weeks of treatment, scores at the 1-year and 2-year follow-up assessments did not differ significantly from baseline scores (p>0.05). One child (PEG+RBV) had a clinically elevated depression score at the 2-year follow-up assessment.[28]
- 13% of PEG+RBV children had neutropenia at week 12; the rate of infections in patients with neutropenia was no different than those without neutropenia.[55] Significant neutropenia (<500 to 750 cells/mm^3) developed in 33% of children and severe neutropenia (250 to 500 cells/mm^3) in 7%` but data was not reported separately for PEG+RBV.[55]
- [i]due to transient blindness, retinal exudates, suicide gesture and new-onset type-1 diabetes, with the latter two considered serious AEs. These side effects were reported as possibly secondary to the drug therapy.
- [j]Schwarz abstract[56] reports early discontinuation of 4%.
- Reports that treatment led to 'significant declines in total white blood cell counts, absolute neutrophil counts and haemoglobin levels which returned to baseline when therapy stopped', but the data are presented in line graphs and not extracted here.
- SVR rates did not differ significantly between patients who had one or more dose reductions and those who had no dose reductions (61% vs 44%, p=0.23).
- 27% of patients required dose reduction for neutropenia but data are not reported separately for PEG+RBV.
- Adherence to 90% of the prescribed doses of PEG and RBV were 100% and 96% respectively.
- [k]Main paper reports that assessments of body composition and growth were performed and will be reported separately (but provides no references).

Methodological comments:

Allocation to treatment groups: Randomisation allocation sequences were generated at a data co-ordinating centre (using a computer-generated randomisation scheme[50]) which determined treatment allocation in a 1:1 ratio. Randomisation was stratified by centre according to genotype (genotype 1 vs non-1). Randomisations were blocked using random blocking factors of 2 and 4 due to the relatively small sample size within each clinical site (~10 participants for each of 11 sites) to best balance the groups.[50]

Allocation concealment: Allocation of each participant to treatment group was conveyed to the centres via a centralised telephone service.

Blinding: Participants, families and investigators were blinded to treatment group. Placebo tablets were supplied in the same dosing regimen as RBV tablets. Does not report whether outcome assessors were blinded.

Analysis by intention to treat: ITT analysis noted for the RCT - all randomised subjects were included in the primary efficacy analysis.

Comparability of treatment groups at baseline: n/a as only using data from one arm (PEG+RBV).

Method of data analysis: A multivariate logistic model was constructed to predict SVR using baseline and results of HCV RNA quantification at 12 weeks. Significance was assessed using a Wald χ^2 comparing the maximum likelihood estimate for each parameter against zero. For ease of presenting odds ratios (OR), continuous variables were dichotomised at their mean. SAS statistical software (version 9.1.3, SAS Institute Inc., Cary, NC) was used for all analyses. Further details are reported in Murray.[50] QoL data: Descriptive statistics were calculated to summarize medical, sociodemographic and outcome variables. Repeated measures ANOVA were

used to assess treatment group and time effects on all outcomes. Clinical decline was operationalized as a >1 SD change in score plus a change in score classification from no impairment at baseline to clinical impairment at 24 weeks; clinical improvement was defined as >1 SD change in score plus a change in score classification from clinical impairment at baseline to no impairment at 24 weeks. To reduce the probability of Type 1 error rate, analyses were initially performed only on the composite or summary scales of the outcome measures. If a statistically significant main or interaction effect emerged, differences on the individual scales were examined for the respective outcome measures. In the final set of analyses, Pearson correlation coefficients and t-tests were calculated to examine the relationship between sociodemographic characteristics and outcomes at the different time points. Due to the large number of tests in this analysis cluster, $p<0.01$ was considered as the level of statistical significance. PAWS (ver. 17.0) statistical software was used for all analyses.[28]
Sample size/power analysis: The RCT was designed to have a statistical power of 80% (standard χ^2 test of equality with 2-sided $\alpha=0.05$) to detect an absolute difference of at least 25% in the proportion achieving SVR in the 2 treatment groups, adjusting for an estimated 15% drop-out rate.[50] It was calculated that 56 patients in each study group were needed to detect a difference of between 25-35%.[50]
Attrition/drop-out: None lost to follow-up (wk 72) but therapy discontinued early in 4/55 (7%) – reasons stated. 7 (13%) lost to follow-up by the 1st annual visit rising to 10 (18%) by the 2nd annual visit.

General comments
Generalisability: Western population, most commonly infected via vertical transmission, who are largely Caucasian with early-stage disease and HCV genotype 1.
Inter-centre variability: not reported
Conflict of interests: Roche provided the drugs and supported the quantitative viral testing but had no role in the study design, oversight, analysis or interpretation. 13 of 17 authors have received support/grants from Roche and other pharmaceutical companies; 1 author is an employee of Roche Molecular Systems; the other 3 authors disclose no conflicts.
Other: Probably the pivotal trial for Peg-2a license approval (Roche).

Quality criteria for assessment of RCTs

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, genotype, viral load`	n/a (used single arm data)
4. Were outcome assessors blinded to the treatment allocation?	Not reported
5. i) Were there any unexpected imbalances in drop-outs between groups? ii) If so, were they explained or adjusted for?	n/a
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes
7. i) Did the analysis include an intention to treat analysis? ii) If so, was this defined?	Yes Yes
8. i) Did the analysis account for missing data? ii) If so, were the methods appropriate?	Unclear

Quality criteria for assessment of uncontrolled, single cohort studies

1. Were the patient selection criteria specified *a priori*?	Yes
2. Was the participant blinded to the treatment?	Yes
3. Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes*
4. Were withdrawals and dropouts completely described?	Yes**
5. i) Did the analysis account for missing data? ii) If so, were the methods appropriate?	Unclear**

*Growth assessed but not reported – stated to be reported later; **Flow chart gives numbers, timing and reasons for dropouts, but unclear whether 4 patients who discontinued the drug were classified as dropouts, and unclear whether they were included in the analysis after drug discontinuation.

Studies of peginterferon α-2a: Sokal and colleagues (2010)[58]

Reference and Design	Intervention	Participants	Outcome measures
Ref ID: #84 **Author:** Sokal *et al*.[58] **Year:** 2010 (study 2003-2005) **Study design**: Single cohort **Number of centres:** 6 **Countries**: Belgium, UK, Sweden, Brazil, Latvia **Funding**: Stated funding was from the drug companies involved; study was partially supported by a grant from the Roche company	**Group 1:** **Drug 1:** PEG IFN α-2a *Dose*: 100µg/m^2 (maximum 180µg) once/weekly by injection. **Drug 2:** Ribavirin *Dose*: 15mg/kg/day (maximum 1200 mg) taken orally *Duration*: Both drugs 24 or 48 weeks according to genotype subgroups (see below) Patients were withdrawn from treatment if HCV PCR assay result was positive at week 24. Stepwise dose reduction was allowed in cases of adverse events (dose-steps reported according to severity), with return to initial doses if adverse events were resolved. **Study design details:** Single-cohort open-label study with patients treated according to genotype in two subgroups: Subgroup A: genotype 2 or 3 treated for 24 weeks Subgroup B: genotype 1, 4, 5 or 6 treated for 48 weeks Both subgroups received the same drugs at the same	**Total numbers involved**: 65 Genotype subgroup A: 18 Genotype subgroup B: 47 **Treatment naïve:** yes (100%) **Previous treatment:** not applicable **HCV/HIV co-infection:** 0 (0%) **Duration of infection:** Not reported **Inclusion criteria**: Treatment-naïve children and adolescents aged 6-17 years with positive anti-HCV serum antibodies and detectable serum HCV RNA. Not limited by levels of serum aminotransferases, HCV genotype, or mode of infection. All patients presenting with hepatitis C were approached for inclusion. Adequate contraception was compulsory (if applicable). **Exclusion criteria:** Pregnancy, anaemia (normal levels according to sex and age), decompensated liver disease, HIV or HBV infection, epilepsy, depression or other poorly controlled psychiatric disease, renal failure, retinopathy, alcohol or drug dependence, or other (unspecified) coexisting medical conditions. **Age (yrs), mean (±SD)**: Overall population: Not reported Subgroup A: 11.3 (3.6) Subgroup B: 12.6 (3.6) **Gender male, n (%)**: Overall population: 30 (46) Subgroup A: 9 (50) Subgroup B: 21 (45) **Weight (kg), mean (±SD):** Overall population: Not reported Subgroup A: 40.9 (3.8) Subgroup B: 43.8 (16.7) **Ethnic groups, n (%)**: Overall population: White 57 (88); Black 2 (3); Asian 1 (2); other 5 (8) Subgroup A: White 17 (94); Black 0 (0); Asian 0 (0); other 1 (6) Subgroup B: White 40 (85); Black 2 (4); Asian 1 (2); other 4 (9)	**Primary outcomes**: SVR (sustained viral response rate) **Secondary outcomes**: EVR (early viral response rate); EOT (end-of-treatment response rate); predictors of virological response; safety (adverse events), growth **Length of follow up**: All patients were followed for 24 weeks after cessation of therapy **Methods of assessing outcomes:** SVR defined as the absence of detectable HCV RNA at the end of the follow up as measured by a PCR assay (Cobas Amplicor™ HCV test, v.2.0; Roche Laboratories) which has a lower limit of detection of 50 IU/ml. EVR defined as the percentage of patients with at least a 2-log drop in HCV RNA levels at week 12 compared to baseline as measured by quantitative real-time PCR assay (Cobas Amplicor™ HCV Monitor v2.0; Roche Laboratories). ETR defined as the percentage of patients with non-detectable HCV RNA at the end of the treatment period (24

	doses	**Mode of infection, n (%)**: Overall population: Vertical: 30 (46) Transfusion: 15 (23) Other: medical procedure: 6 (9) Unknown: 14 (22) Subgroup A: Vertical: 10 (56) Transfusion: 7 (39) Other: medical procedure: 0 (0) Unknown: 1 (6) Subgroup B: Vertical: 20 (43) Transfusion: 8 (17) Other: medical procedure: 6 (13) Unknown: 13 (28) **Genotypes, n (%)**: 1: 45 (69) 2: 2 (3) 3: 16 (25) 4: 1 (2) 5 or 6: 1 (2) **Sample attrition/dropout, n (%)**: 10 (15) all of whom were in subgroup B: No virologic response at week 24: 8 (12) Serious adverse event: 2 (3) Other violation: 0 (0)	or 48 weeks according to the genotype subgroup). Liver fibrosis: classification system not reported

Definitions/comments:

Participant characteristics /outcomes	**Baseline**	**Post-treatment**	
HCV RNA (IU/ml), n (rounded %)			
Overall population:			
<500,000	23 (36)	Not reported	
>500,000	42 (65)	Not reported	
Subgroup A:			
<500,000	10 (56)	Not reported	
>500,000	8 (44)	Not reported	
Subgroup B:			
<500,000	13 (28)	Not reported	
>500,000	34 (72)	Not reported	
Serum ALT (IU/L), mean (±SD):	Not reported [a]	Not reported	
Fibrosis score, n/N (%):	needs checking		
Overall population: No fibrosis	34/65 (52)	Not reported	
Fibrosis:	30/65 (46)	Not reported	
Grade F1	21/65 (32)	Not reported	
Grade F2	9/65 (14)	Not reported	
Subgroup A: No fibrosis	8/18 (44)	Not reported	
Fibrosis:	10/18 (56)	Not reported	

Grade F1	7/18 (39)	Not reported	
Grade F2	3/18 (17)	Not reported	
Subgroup B:[b] No fibrosis	26/47 (55%)	Not reported	
Fibrosis:	20/47 (43)	Not reported	
Grade F1	14/47 (30)	Not reported	
Grade F2	6/47 (13)	Not reported	
Necroinflammatory score, mean (±SD):	Not reported	Not reported	

Notes/comments:
[a] Serum ALT concentration not reported; ALT quotient and ALT ratio vs normal were reported (baseline only) (data not extracted)
[b]No biopsy was taken in one patient (with haemophilia)

Outcomes	**Baseline**	**Post-treatment**	**p-value**
Viral Response, % (n/N) RVR (4 wk):	n/a	Not reported	
EVR (12 wk): Overall population:	n/a	65 (42/65) (3ND) [a]	See notes [b]
Subgroup A:	n/a	83 (15/18) (2 ND)	
Subgroup B:	n/a	57 (27/47) (1 ND)	p<0.05
EOT (End of treatment): Overall population:	n/a	68 (44/65) (2 ND) [a]	See notes [b]
Subgroup A:	n/a	94 (17/18) (1 ND)	
Subgroup B:	n/a	57 (27/47) (1 ND)	p<0.001
SVR (End of follow-up): Overall population:	n/a	66 (43/65) (2 ND) [a]	See notes [b]
Subgroup A:	n/a	89 (16/18) (1 ND)	
Subgroup B:	n/a	57 (27/47) (1 ND)	p<0.01

Notes/comments:
[a] Data were reported for subgroups A and B, from which the overall population data were calculated by the reviewer. Response rates were reported inconsistently in the text and tables of the primary publication, with "ND" patients both included in and excluded from calculations of percentage response rates. For consistency, the data extracted above are based on all patients in each group, irrespective of the number classified as "ND". The meaning of "ND" was not stated – presumed to mean that the viral response was not determined.
[b] Statistical p-values were reported but it was not stated to which comparisons they apply (data not extracted as unclear). Text at top of p.828 reports a statistical difference in SVR between subgroup A vs B (i.e. genotype 2/3 vs 1,4,5,6). Also, the abstract reports the statistical differences are between the genotype subgroups for EVR ($p<0.05$), EOT ($p<0.001$) and SVR ($p<0.01$).
Reports EVR as a predictor of SVR but not extracted here.

SVR subgroup data, rounded % (n/N):			
SVR by EVR:			
Overall population	n/a	85 (35/42) [c]	
Subgroup A	n/a	93 (13/14)	
Subgroup B	n/a	81 (22/27)	
SVR by no EVR	n/a	30 (6/20)	
SVR by baseline viral load			
Overall population:			
$<5 \times 10^5$ IU/ml	n/a	74 (17/23)	
$>5 \times 10^5$ IU/ml	n/a	55 (22/40)	

Subgroup A:			
$<5 \times 10^5$ IU/ml	n/a	90 (9/10)	
$>5 \times 10^5$ IU/ml	n/a	100 (7/7)	
Subgroup B:			
$<5 \times 10^5$ IU/ml	n/a	62 (8/13)	
$>5 \times 10^5$ IU/ml	n/a	45 (15/33)	
SVR by ALT screening			
Baseline ALT normal	n/a	80 (24/30)	
Baseline ALT abnormal	n/a	58 (19/33)	
SVR by histology			
Baseline no fibrosis	n/a	76 (25/33)	
Baseline fibrosis	n/a	60 (18/30)	
SVR by genotype and ALT			
Subgroup A:			
Baseline ALT normal	n/a	89 (8/9)	
Baseline ALT abnormal	n/a	100 (8/8)	
Subgroup B:			
Baseline ALT normal	n/a	89 (17/19)	
Baseline ALT abnormal	n/a	37 (10/27)	See notes [e]
SVR by genotype and fibrosis			
Subgroup A:			
Baseline no fibrosis	n/a	100 (8/8)	
Baseline fibrosis	n/a	89 (8/9)	
Subgroup B:			
Baseline no fibrosis	n/a	68 (17/25)	
Baseline fibrosis	n/a	48 (10/21)	
Other viral response outcomes:	n/a	No additional outcomes reported	
Non-response, % (n/N): Overall population	n/a	12 (8/65)	
Subgroup A	n/a	0 (0/18)	
Subgroup B	n/a	17 (8/47)	

Notes/comments:

[c] Data were reported for subgroups A and B, from which the overall population data were calculated by the reviewer; numbers sum to 41 but should sum to the number of patients with an EVR which was 42 (the reason for this discrepancy is unclear but may reflect one "ND" patient not being specified in the reported data).

[d] As noted above, response rates were reported inconsistently in the primary publication; the data extracted here are for all patients in each group, irrespective of the number classified as "ND"

[e] Statistical p-values were reported but it was not stated to which comparisons they apply (data not extracted into table as unclear). Text at top p.828 states SVR was 89% in those with genotypes 1, 4, 5 or 6 and normal baseline ALT compared to 36% (37% in table) for those with abnormal ALT ($p<0.001$), thus statistical comparison is within the genotype subgroup.

Quality of life outcomes	Not reported	Not reported	
Adverse Events, % (n/N) Dose discontinuation for serious AE (acute hepatitis, laboratory abnormality/ thyreotoxicosis)	n/a	3 (2/65)	
Dose discontinuation due to non-response at 24 weeks	Same numbers as for non-response above	Same numbers as for non-response above	
PEG IFN dose reduction for AE [f] Overall population:	n/a	23 (15/65)	
Subgroup A:	n/a	22 (4/18)	
Subgroup B:	n/a	23 (11/47)	

Overall population, by event:			
Neutropenia	n/a	17 (11/65)	
Thrombocytopenia	n/a	1.5 (1/65)	
Laboratory anomaly	n/a	1.5 (1/65)	
Asthenia	n/a	1.5 (1/65)	
Non-response to treatment	n/a	1.5 (1/65)	
Ribavirin dose reduction for AE [e]			
Anaemia, overall population	n/a	5 (3/65)	
Subgroup A	n/a	0 (0/18)	
Subgroup B	n/a	6 (3/47)	
Serious adverse events, % (n/N)			
Acute hepatitis	n/a	1.5 (1/65)	
Thyreotoxicosis	n/a	1.5 (1/65)	
Urinary tract infection	n/a	1.5 (1/65)	
Pulmonary hypertension	n/a	1.5 (1/65)	
Specific adverse events, % (n/N)			
Fever/flu-like symptoms	n/a	54 (35/65)	
Headache	n/a	45 (29/65)	
Abdominal pain	n/a	38 (25/65)	
Fatigue	n/a	34 (22/65)	
Irritability/depression/mood change (no suicidal ideation)	n/a	34 (22/65)	
Dermatitis	n/a	29 (19/65)	
Nausea/vomiting	n/a	23 (15/65)	
Infection	n/a	23 (15/65)	
Viral	n/a	9 (6/65)	
Bacterial	n/a	14 (9/65)	
Decreased appetite	n/a	21.5 (14/65)	
Insomnia	n/a	18 (12/65)	
Sore throat	n/a	15 (10/65)	
Diarrhoea	n/a	14 (9/65)	
Injection site pain/erythema/ local infection	n/a	14 (9/65)	
Dyspnoea	n/a	11 (7/65)	
Thyroid hormone problems, overall population	n/a	11 (7/65)	
Subgroup A	n/a	0 (0/18)	
Subgroup B	n/a	15 (7/47)	
Myalgia	n/a	9 (6/65)	
Alopecia	n/a	9 (6/65)	
Bleeding	n/a	9 (6/65)	
Pruritis	n/a	6 (4/65)	
Arthralgia	n/a	3 (2/65)	
Enuresis/dysuria	n/a	3 (2/65)	
Palpitations	n/a	3 (2/65)	
Mortality, % (n/N)	n/a	Not reported (=none)	
Effects on growth			
Weight, Z-score	-0.3 ± 0.9	-0.3 ± 1.0	Stated NS
Height, Z-score	-0.4 ± 1.0	-0.5 ± 1.1	Stated NS

Notes/comments:
[f] Stated in abstract that dose adjustments due to AE were made in 15 patients, however data are only reported for 14 patients
NS: not statistically significant

Methodological comments: Note if n/a.
Allocation to treatment groups: n/a: single-cohort study
Allocation concealment: n/a
Blinding: None (stated open label)
Analysis by intention to treat: n/a: non-randomised study (stated that primary analysis had an 'intent-to-treat' approach but no further details reported)
Comparability of treatment groups at baseline: n/a (the two subgroups were reported to be similar, except for pre-treatment viral load which was higher in group B)
Method of data analysis: Fisher's exact test (misspelt) used but the groups being compared were not stated
Sample size/power analysis: Not reported
Attrition/drop-out: Reported with reasons

General comments
Generalisability: Treatment-naïve children and adolescents aged 6-17 years, genotypes 1-6, of predominantly white ethnicity, with positive anti-HCV serum antibodies and detectable serum HCV RNA. Not limited by levels of serum aminotransferases, HCV genotype, or mode of infection. Duration of HCV infection unclear.
Inter-centre variability: Not reported.
Conflict of interests: Funding was from the drug manufacturer (Roche)

Quality criteria for assessment of uncontrolled, single cohort studies

1. Were the patient selection criteria specified *a priori*?	Yes
2. Was the participant blinded to the research question?	N/a
3. Is there any evidence to suggest that the authors measured more outcomes than they reported?	Unclear
4. Were withdrawals and dropouts completely described?	Yes
5. i) Did the analysis account for missing data? ii) If so, were the methods appropriate?	Unclear (test reported but not the groups being compared)

Studies of peginterferon α-2b: Al Ali and colleagues (2010)[46]

Reference and Design	Intervention	Participants	Outcome measures
Ref ID: #82 **Author:** Al Ali *et al*.[46] **Year:** 2010 (study dates not reported) **Study design**: Single cohort **Number of centres:** 1 (not explicitly stated) **Country**: Kuwait **Funding**: Stated that no financial support was used for this work	**Group 1:** **Drug 1: PEG IFN α-2b** *Dose*: 1.5µg/kg per week by sub-cutaneous injection *Duration*: 48 weeks **Drug 2: Ribavirin** *Dose*: 15 mg/kg/day taken orally *Duration*: 48 weeks PEG IFN α-2b was administered in the local primary care clinic by a registered nurse who documented compliance. Adherence to ribavirin ingestion was monitored by capsule count. Stepwise reductions in treatments were permitted for management of adverse events and laboratory abnormalities (no further details reported) **Study design details:** Open-label uncontrolled single-cohort study described as a pilot study	**Total numbers involved**: 12 **Treatment naïve:** Yes (100%) **Previous treatment:** n/a **HCV/HIV co-infection:** Not reported **Duration of infection:** Not reported **Inclusion criteria**: Treatment-naïve patients aged 14-17 years with detectable HCV RNA, genotype 4 and anti-HCV positive liver biopsy findings consistent with the diagnosis of chronic hepatitis C, for whom a decision to treat was made. Patients were included independent of mode of acquisition of infection, level of serum aminotransferases, or serum HCV RNA viral load. **Exclusion criteria:** Clinical or biochemical evidence of hepatic decompensation, severe psychiatric disorders, haemoglobin <100 g/L, white blood cell count <2,500/mm^3, platelet counts <70.000/mm^3 and serum creatinine >200 mmol/L. **Age (yrs), mean range)**: 15.75 (14-17) **Gender male, n (%)**: 8 (67) **Weight or BMI:** Not reported **Ethnic groups, n (%)**: Not explicitly stated but implied Middle Eastern (study in Kuwait) **Mode of infection, n (%)**: Vertical: 2 (17) IV drug use: 2 (17) Transfusion: 1 (8) Other: dental procedures: 2 (17) Unknown: 5 (42) **Genotypes, n (%)**: 4: 12 (100) **Sample attrition/dropout**: 11 patients (92%) completed the study. The patient who dropped out developed type 1 diabetes mellitus	**Primary outcomes**: Sustained virological response (SVR) **Secondary outcomes**: Early virological response (EVR); End-of-treatment response (EOT); Adverse events **Length of follow up**: 24 weeks post-treatment **Methods of assessing outcomes:** SVR was defined as an undetectable (<50 IU/mL) HCV RNA after 24 weeks of treatment-free follow-up (week 72). EVR was defined as HCV RNA <50 IU/mL at week 12 of therapy. EOT response was defined as HCV RNA <50 IU/mL at week 48. Serum HCV RNA testing was performed using a qualitative PCR assay (Cobas Amplicor HCV Test v. 2.0; Roche Diagnostics). Liver histology was graded using the METAVIR scoring system (no details provided).
Definitions/comments:			

Participant characteristics /outcomes	**Baseline**	**Post-treatment**	
HCV RNA (×10^6 IU/ml), mean (range):	0.78 (0.23-1.8)	Not reported	
Serum ALT (IU/L), mean range):	91 (34-194)	Not reported	
Fibrosis score, mean (range): METAVIR histological grade [a]	1.67 (1-2)	Not reported	
METAVIR fibrosis score [a]	0.67 (0-3)	Not reported	
Necroinflammatory score, mean (±SD):	Not reported	Not reported	
Notes/comments: [a] METAVIR scoring system not described ALT: alanine transferase			
Outcomes	**Baseline**	**Post-treatment**	**p-value**
Viral Response, % (n/N) RVR (4 wk):	n/a	Not reported	
EVR (12 wk)	n/a	83 (10/12)	
EOT (End of treatment):	n/a	83 (10/12)	
SVR (End of follow-up; week 72):	n/a	75 (9/12)	
Notes/comments:			
SVR subgroup data, % (n/N): add/delete as necessary	n/a	Not reported	
SVR by EVR	n/a	100 (10/10)	
Non-response, % (n/N):	n/a	17 (2/12) [b]	
Relapse, % (n/N):	n/a	8 (1/12) [c]	
Notes/comments: [b] The two non-responders had baseline HCV RNA levels that were higher than those of most other patients (1.1 and 1.8 × 10^6 IU/mL) [c] This patient relapsed during the third month of follow-up having achieved an EOT response			
Quality of life outcomes	Not reported	Not reported	
Adverse Events, % (n/N) Dose discontinuation for any AE:	n/a	Not reported (see comment below about compliance)	
Dose discontinuation for other reason:	n/a	Not reported	
Dose reduction for any AE:	n/a	Not reported	
Dose reduction for anaemia	n/a	33 (4/12) (see notes below)	
Dose reduction for neutropenia:	n/a	Not reported	
Dose reduction for other:	n/a	Not reported	
Specific adverse events, % (n/N)			
Fever/flu-like symptoms	n/a	100 (12/12)	
Leucopenia	n/a	67 (8/12) [d]	
Myalgia	n/a	58 (7/12)	
Anaemia < 10 g/L	n/a	33 (4/12) [e]	
Neutropenia	n/a	17 (2/12)	
Type 1 diabetes mellitus	n/a	8 (1/12)	
Hypothyroidism	n/a	8 (1/12)	
Insomnia	n/a	8 (1/12)	
Mortality, % (n/N)	Not reported	Not reported	
Effects on growth	Not reported	Not reported	

Notes/comments:
Compliance: Stated that all 11 patients who completed the study took at least 80% of the Peg IFN α-2b and ribavirin
[d] Only one of the patients with leucopenia required treatment with growth factors
[e] Three of the four patients with anaemia were females who had coincidental menorrhagia; stated that the dose of ribavirin for these patients was reduced (by an unspecified amount) when haemoglobin was below 10 g/dL; stated (in abstract) that the fourth person with anaemia also had ribavirin dose reduction

Methodological comments: Note if n/a.
Allocation to treatment groups: n/a
Allocation concealment: n/a
Blinding: None (stated open label)
Analysis by intention to treat: n/a
Comparability of treatment groups at baseline: n/a
Method of data analysis: None reported: results presented narratively
Sample size/power analysis: Not reported
Attrition/drop-out: Reported with reasons

General comments
Generalisability: Genotype 4 treatment-naïve patients likely of Middle Eastern ethnicity with mild liver disease with low pre-treatment viral load
*Inter-centre variability:*Not applicable (single centre)
Conflict of interests: Stated only that no funding was provided; no declaration of interests given in the paper.

Quality criteria for assessment of uncontrolled, single cohort studies

1. Were the patient selection criteria specified *a priori*?	Yes
2. Was the participant blinded to treatment?	N/a
3. Is there any evidence to suggest that the authors measured more outcomes than they reported?	Unclear
4. Were withdrawals and dropouts completely described?	Yes
5. i) Did the analysis account for missing data? ii) If so, were the methods appropriate?	Unclear (no formal analysis conducted)

Studies of peginterferon α-2b: Pawlowska and colleagues (2010)[52]

Reference and Design	Intervention	Participants	Outcome measures
Ref ID: #60 and abstract #841 **Author:** Pawlowska *et al*.[52;53] **Year:** 2010 (abstract 2008) **Study design**: Single cohort study **Number of centres:** 1 (not explicitly stated) **Country**: Poland **Funding**: States 'departmental sources'	**Group 1:** **Drug 1:** PEG IFN α-2b *Dose*: 1.5µg/kg/wk by subcutaneous injection *Duration*: 48 weeks[a] **Drug 2:** Ribavirin *Dose*: 15 mg/kg/d taken orally *Duration*: 48 weeks[a] **Study design details:** Single uncontrolled cohort but children were 'divided' into 2 groups according to previous treatment (treatment naïve and previously treated). Baseline characteristics and most results are presented for the whole cohort as well as separately for the 2 subgroups. [a]Several sections state that all patients received PEG+RBV for 48 weeks; however the beginning of the Methods section also states that patients were treated for 24 weeks (genotype 3) or 48 weeks (genotypes 1 & 4).	**Total numbers involved**: 53 (29 treatment naïve; 24 previously treated) **Treatment naïve:** 29 (54%) **Previous treatment:** 24 (46%) treated with IFN α-2b + RBV for 12 months, 2-5 years earlier (10 relapsers, 8 non-responders, 6 breakthroughs) **HCV/HIV co-infection:** none **Duration of infection (mean ± SD):** 5.4 ± 3.6 years (4.12 ± 3.7 naïve; 6.92 ± 2.8 treated) Abstract reports mean duration 8.5 ± 4.6 years.[53] **Inclusion criteria**: Children aged 8 to 17 years with chronic hepatitis C diagnosed by the presence of serum HCV RNA and histopathological changes in the liver. All children had a liver biopsy and ultrasound. **Exclusion criteria:** histological evidence of hepatocellular carcinoma, chronic liver disease other than chronic hepatitis C, co-infection with hepatitis B or HIV. **Age (yrs), mean ± SD (range)**: All: 13.6 ± 2.4 (8-17) **Gender male, n (%)**: All: 37 (70%) [20 naïve, 17 treated] **Ethnic groups, n (%)**: not reported **Mode of infection, n:**[b] Vertical: 0 Transfusion: 5 (1 naïve, 4 treated) Hospital-acquired: 53 (29 naïve, 24 treated) Surgical procedure: 16 (7 naïve, 9 treated) [b]More than one mode of transmission of HCV as numbers exceed 53 (100%) **Genotypes, n (%)**: All 1: 27 (50%) [16 naïve, 11 treated] 2: 0 3: 2 (4%) [both naïve] 4: 24 (46%) [11 naïve, 13 treated] **Sample attrition/dropout**: none reported	**Primary outcomes**: SVR **Secondary outcomes**: EVR (partial and complete), EOT virological response, relapse, breakthrough, non-response, predictors of virological response, adverse events, growth (v brief narrative only) **Length of follow up**: 24 wks after end of treatment. SVR was also measured 24 months after SVR assessment (little data presented) and follow-up for assessment of growth is ongoing (plan is for 5 years) **Methods of assessing outcomes:** Blood samples to determine HCV RNA viral load & ALT activity performed at each clinic visit. Serum HCV RNA viral load determined at baseline, weeks 12 & 48 during treatment, and after 24 weeks of untreated follow-up by quantitative PCR assay (COBAS AmpliPrep/ COBAS TaqMan HCV Test Roche, Geneva, Switzerland, with a limit of detection of 43 IU/ml. SVR defined as undetectable HCV RNA in serum 24 weeks after the end of treatment. EVR defined as HCV RNA viral load at week 12 of treatment; complete EVR -

			undetectable serum HCV RNA at week 12; partial EVR - a decrease of HCV RNA of >2 logs relative to baseline. EOT defined as undetectable serum HCV RNA at week 48 of treatment. Relapse defined as appearance of HCV RNA at week 72 after undetectable serum HCV RNA at week 48. Histology classification system used: modified Scheuer scale HCV genotypes defined using the INNOGENETICS INNO-LiPA HCV II test. Safety was monitored at each clinic visit by lab tests, physical examination and adverse events reported by the patient or guardian.

Definitions/comments: EOT, end of treatment; EVR, early viral response; PCR, polymerase chain reaction; SVR, sustained virological response.

Participant characteristics /outcomes	**Baseline**	**Post-treatment**	
HCV RNA (IU/ml), mean (±SD):			
All[c]	4.56 $x10^5$	Not reported	
Naïve	4.35 ± 3.09 $x10^5$	Not reported	
Treated	5.16 ± 2.12 $x10^5$	Not reported	
HCV RNA, n/N (%):[d]			
All: <500,000 IU/mL	21/53 (40%)	Not reported	
>500,000 IU/mL	29/53 (55%)	Not reported	
Naïve: <500,000 IU/mL	12/53 (23%); 12/29 (41%)[e]	Not reported	
>500,000 IU/mL	15/53 (28%); 15/29 (52%)[e]	Not reported	
Treated: <500,000 IU/mL	9/53 (17%); 9/24 (38%)[e]	Not reported	
>500,000 IU/mL	14/53 (26%); 14/24 (58%)[e]	Not reported	
Serum ALT (U/L), mean (±SD):			
All:	45.8 ± 24.3	Not reported	
Naïve:	48.0 ± 29.0	Not reported	
Treated:	43.0 ± 21.0	Not reported	
Fibrosis score, modified Scheuer scale stages 0 to 4:			
All	≤ stage 2	Not reported	

Necroinflammatory score, modified Scheuer scale grades 0 to 4: All	≤ grade 2	Not reported	
Notes/comments: [c]SD not reported; [d]3 patients not accounted for (assessed only qualitatively); [e]proportion within subgroup (calculated by reviewer).			
Outcomes	**Baseline**	**Post-treatment**	**p-value**
Viral Response, % (n/N) **RVR:**	n/a	Not reported	
EVR[f]: All	n/a	77.4% (41/53)	
Naïve	n/a	86.2% (25/29)	
Treated	n/a	66.7% (16/24)	
EOT: All	n/a	66% (35/53)	
Naïve	n/a	65% (19/29)	
Treated	n/a	66.7% (16/24)	
SVR: All	n/a	49.1% (26/53)[g]	
Naive	n/a	62.1% (18/29)	
Treated	n/a	33.3% (8/24)	
Notes/comments: [f]data for complete EVR and partial EVR were reported but have not been data extracted here. [g]Abstract reports an SVR of 47% for whole group.[53]			
SVR subgroup data, % (n/N): *SVR by genotype* Genotype 1: All	n/a	48% (13/27)	
Naïve	n/a	62% (10/16)	
Treated	n/a	27% (3/11)	
Genotype 3 (both naïve)	n/a	50% (1/2)	
Genotype 4: All	n/a	50% (12/24)	
Naïve	n/a	72% (8/11)	
Treated	n/a	30% (4/13)	
Relapse, % (n/N): All	n/a	17.0% (9/53)[h]	
Naive	n/a	3.4% (1/29)[h]	
Treated	n/a	33.3% (8/24)	
Breakthrough, % (n/N): All	n/a	11% (6/53)	
Naïve	n/a	20% (6/29)	
Treated	n/a	0	
Non-response, % (n/N): All	n/a	50.9% (27/53)	
Naive	n/a	37.9% (11/29)	
Treated	n/a	66.7% (16/24)	

Notes/comments:

- Reports that there were no statistically significant differences in SVR according to HCV 1 and 4 genotypes (chi-square test) and that the number of children with HCV genotype 3 excluded them from the statistical analyses.
- [h]Abstract reports a relapse rate of 7.5% in whole group, 5.6% in Naïve group and 33% in Treated group.[53]
- Predictors of treatment response were also reported but data has not been extracted here. The most important predictor of SVR in both groups was complete EVR ($p<0.001$, chi-square test) – all children who achieved a complete EVR achieved an SVR. Relapses occurred in 1/7 children (Naïve) and 8/8 children (Treated) who had partial EVR.
- Levels of baseline serum HCV RNA were statistically significantly lower in children who achieved an SVR (responders) than in those who did not (non-responders) ($p<0.05$).
- Baseline ALT activity in responders was slightly higher, but the difference was not statistically significant.
- In all children who achieved an SVR, HCV RNA remained undetectable at 24 months after assessing SVR (an additional 2 years).

Quality of life outcomes	n/a	Not reported	
Adverse Events, % (n/N)			
Dose discontinuation for any AE	n/a	Not reported	
Dose discontinuation for other reason	n/a	Not reported	
Dose reduction for any AE	n/a	Not reported	
Dose reduction (RBV) for anaemia			
All	n/a	6% (3/53)	
Naive	n/a	10% (3/29)	
Dose reduction for neutropenia	n/a	Not reported	
Dose reduction for other	n/a	Not reported	
Specific adverse events, % (n/N)[i]			
Flu-like syndrome:			
All	n/a	66.0% (35/53)	
Naive	n/a	55.2% (16/29)	
Treated	n/a	79.2% (19/24)	
Leuokopenia:			
All	n/a	64.2% (34/53)	
Naïve	n/a	65.5% (19/29)	
Treated	n/a	62.5% (15/24)	
Fever:			
All	n/a	50.2% (27/53)	
Naïve	n/a	55.2% (16/29)	
Treated	n/a	45.8% (11/24)	
Headache:			
All	n/a	45.3% (24/53)	
Naïve	n/a	27.6% (8/29)	
Treated	n/a	66.7% (16/24)	
Weight loss >10%:			
All	n/a	43.4% (23/53)	
Naïve	n/a	34.5% (10/29)	
Treated	n/a	54.2% (13/24)	
Local reaction:			
All	n/a	34.0% (18/53)	
Naïve	n/a	20.7% (6/29)	
Treated	n/a	50.0% (12/24)	
Anaemia:			
All	n/a	24.5% (13/53)	
Naïve	n/a	24.1% (7/29)	
Treated	n/a	25.0% (6/24)	

Abdominal pain: All	n/a	20.8% (11/53)	
Naïve	n/a	3.4% (1/29)	
Treated	n/a	41.7% (10/24)	
Neurasthenia:[j] All	n/a	20.8% (11/53)	
Naïve	n/a	13.8% (4/29)	
Treated		29.2% (7/24)	
Hair loss: All	n/a	20.8% (11/53)	
Naïve	n/a	24.1% (7/29)	
Treated	n/a	16.7% (4/24)	
Thrombocytopenia: All	n/a	15.1% (8/53)	
Naïve	n/a	20.7% (6/29)	
Treated	n/a	8.3% (2/24)	
Mortality, % (n/N)	n/a	Not reported	
Effects on growth[k] All	n/a	"No influence on height at follow-up or 2 years after follow-up"	

Notes/comments:

- [i]Percentages for Naïve and Treated groups calculated by reviewer.
- [j]Neurasthenia included irritability, change of mood and depression.
- States no adverse events were observed following IFN dose reductions; however, numbers of patients requiring IFN modifications were not reported.
- In almost all children, a flu-like syndrome of variable intensity was observed during the first weeks of treatment but symptoms resolved for most in the second half of the year.
- Leukocyte counts decreased during the first 4 weeks of treatment, and the majority of patients were below the normal range during treatment, increasing to baseline values post-treatment.
- Authors state that there are plans to assess growth of treated patients 5 years after treatment cessation but give no further details.

Methodological comments:
Allocation to treatment groups: n/a
Allocation concealment: n/a
Blinding: None (stated open uncontrolled study)
Analysis by intention to treat: n/a
Comparability of treatment groups at baseline: n/a. However, baseline characteristics were presented separately for the Naïve and Treated subgroups (as well as whole group) – Naïve patients appeared to have lower baseline HCV RNA, shorter duration of infection and higher proportion with genotype 1, but no statistical comparisons were reported. All other characteristics appear comparable.
Method of data analysis: Serum HCV RNA were analysed by descriptive statistics. Reports that means and SDs were calculated at the various time points during treatment and follow-up. Virological response outcomes were presented as proportions (n, %). States that the *t*-test, Mann-Whitney *U* and chi-square tests were used to compare 'examined groups' - unclear whether this refers to Naïve and Treated groups or genotype groups or those achieving/not achieving SVR. Few statistics are reported for the main outcomes. Children with genotype 3 were excluded from the statistical analyses.
Sample size/power analysis: None reported
Attrition/drop-out: None reported

General comments
Generalisability: Polish population, treatment naïve and previously treated mixture of patients, with largely hospital-acquired mode of infection. 55% have a higher baseline HCV RNA viral load, approximately half are

previously treated and most are genotype 1 or 4.
Inter-centre variability: single-centre study
Conflict of interests: none reported
Other: None

Quality criteria for assessment of uncontrolled, single cohort studies

1. Were the patient selection criteria specified *a priori*?	Yes
2. Was the participant blinded to the treatment?	N/a
3. Is there any evidence to suggest that the authors measured more outcomes than they reported?	Unclear
4. Were withdrawals and dropouts completely described?	Not reported
5. i) Did the analysis account for missing data? ii) If so, were the methods appropriate?	No

Studies of peginterferon α-2b: Wirth and colleagues (2010)[60]

Reference and Design	Intervention	Participants	Outcome measures
Ref ID: #94 and abstract #836 **Author:** Wirth *et al*.[59;60] **Year:** 2010 (study dates not reported) **Study design**: Single cohort **Number of centres:** 22 **Countries**: Austria, France, Germany, Italy, Spain, Argentina, Chile, USA, Puerto Rico **Funding**: 25 of the 32 authors received funding from the drug manufacturer (Schering-Plough); 6 authors were employed by the drug manufacturer; support for writing the	**Group 1:** **Drug 1: PEG IFN α-2b** *Dose*: 60 µg/m^2 per week **Drug 2: Ribavirin** *Dose*: 15 mg/kg/day *Duration*: Both drugs 24 or 48 weeks according to genotype and viral load (see subgroups below) Pre-specified dose reduction and discontinuation criteria: PEG IFN α-2b dose reduced if neutrophil count <750/mm^3 or platelet count <70,000/mm^3; ribavirin dose reduced if haemoglobin <10 g/dL. Both drugs discontinued if neutrophil count <500/mm^3; platelet count <50,000/mm^3; or haemoglobin <8.5 g/dL. Two-step dose reductions were used: PEG IFN α-2b reduced initially to 40µg/m^2 weekly then if needed to 20µg/m^2. Ribavirin reduced initially to 12 mg/kg/day then if needed to 8 mg/kg/day. **Study design details:** Single cohort with two subgroups according to genotype and viral load: Subgroup A (n=27): genotypes 2 and 3 with low baseline viral load (<600,000 IU/mL)	**Total numbers involved**: 107 (1-12 patients per centre) Subgroup A: 27; Subgroup B: 80 Baseline characteristics were presented for all patients and also separately for ages 3-11 years (n=67) and 12-17 years (n=40) **Treatment naïve:** Yes (100%) **Previous treatment:** Not applicable **HCV/HIV co-infection:** No (100%) **Mean ± SD duration of infection, years:** Overall: 8.5 ± 4.2 Ages 3-11 yrs: 6.5 ± 2.5 Ages 12-17 yrs: 12.3 ± 4.1 **Inclusion criteria**: Children aged 3-17 years with previously untreated chronic hepatitis C; absolute neutrophil count ≥ 1500/mm^3; platelet count ≥ 100,000/mm^3; and haemoglobin levels ≥ 11 g/dL for girls and 12 g/dL for boys. Evidence of fibrosis and/or inflammatory activity from liver biopsy was requested from all patients before enrollment; however a waiver was permitted for children aged 3-11 years who had an elevated ALT in the year before screening. **Exclusion criteria:** (stated as the 'key' exclusion criteria, which may indicate there were others): Decompensated liver disease; coexisting HBV or HIV infection; haemoglobinopathy; haemophilia; malignant or immunologic diseases; neurologic or psychiatric disorders; retinopathy; substance abuse; chronic cardiopulmonary disease; immunosuppressive treatment. Patients with body weight >90 kg were also excluded. **Age (yrs), mean**: Overall: 10 Ages 3-11 yrs: 7 Ages 12-17 yrs: 14 **Gender male, n (%)**: Overall: 51 (48) Ages 3-11 yrs: 27 (40) Ages 12-17 yrs: 24 (60) **Weight or BMI:** Not reported **Ethnic groups: white, n (%)**:	**Primary outcome**: Sustained virologic response (SVR) **Secondary outcomes**: Rapid virologic response (RVR), early virologic response (EVR), predictors of virological response, relapse, biochemical response, adverse events, growth **Length of follow up**: 24 weeks after end of therapy. Patients with <2 $\log_{10}$ drop in HCV-RNA in week 12 or detectable HCV RNA at week 24 discontinued therapy and entered follow-up. **Methods of assessing outcomes:** SVR was defined as undetectable HCV RNA 24 weeks after completion of therapy. RVR was defined as undetectable HCV RNA at treatment week 4. EVR was defined as undetectable HCV RNA at treatment week 12. Relapse was defined as undetectable HCV RNA at the last treatment visit and detectable HCV RNA at the last follow-up visit. Biochemical response was defined as normalisation of ALT levels among patients with elevated ALT at

manuscript was also provided by the drug manu-facturer	were treated for 24 weeks. Subgroup B (n=80): genotypes 1, 3, 4 with high baseline viral load (≥600,000 IU/mL were treated for 48 weeks. Trial registration numbers: NCT00104052 NCT00761735	Overall: 95 (89) Ages 3-11 yrs: 60 (90) Ages 12-17 yrs: 35 (88) **Mode of infection, n (%)**: Overall: Vertical: 75 (70) Parenteral / transfusion: 12 (11) Sporadic / other (not specified): 20 (19) Ages 3-11 yrs: Vertical: 52 (78) Parenteral / transfusion: 4 (6) Sporadic / other (not specified): 11 (16) Ages 12-17 yrs: Vertical: 23 (58) Parenteral / transfusion: 8 (20) Sporadic / other (not specified): 9 (23) **Genotypes, n (%):** Overall: 1: 72 (67); 2: 15 (14); 3: 15 (14); 4: 5 (5) Ages 3-11 yrs: 47 (70); 6 (9); 10 (15); 4 (6) Ages 12-17 yrs: 25 (63); 9 (23); 5 (13); 1 (3) **Sample attrition/dropout**: Outcomes were reported for all patients who started therapy (N=107). One patient discontinued therapy due to thrombocytopenia at 42 weeks.	baseline. Plasma HCV RNA was measured using a proprietary assay: TaqMan; Schering-Plough; lower limit of detection 125 IU/mL. Liver biopsy slides were assessed using METAVIR fibrosis and activity scores Adverse events were graded as mild, moderate or severe

Definitions/comments:
ALT: alanine aminotransferase

Participant characteristics /outcomes	**Baseline**	**Post-treatment**	
HCV RNA (IU/ml), overall:			
Geometric mean	442,748	Not reported	
<600,000 IU/mL, % (n/N)	54 (58/107)	Not reported	
>600,000 IU/mL, % (n/N)	42 (45/107)	Not reported	
Missing, n(%)	4 (4/107)	Not reported	
Ages 3-11 yrs:			
Geometric mean	398,107	Not reported	
<600,000 IU/mL, % (n/N)	57 (38/67)	Not reported	
>600,000 IU/mL, % (n/N)	40 (27/67)	Not reported	
Missing, n(%)	3 (2/67)	Not reported	
Ages 12-17 yrs:			
Geometric mean	531,018	Not reported	
<600,000 IU/mL, % (n/N)	50 (20/40)	Not reported	
>600,000 IU/mL, % (n/N)	45 (18/40)	Not reported	
Missing, n(%)	5 (2/40)	Not reported	
Serum ALT (IU/L), overall:			
Normal, % (n/N)	59 (63/107)	Not reported	
Abnormal, % (n/N)	41 (44/107)	Not reported	

Ages 3-11 yrs:			
Normal, % (n/N)	55 (37/67)	Not reported	
Abnormal, % (n/N)	45 (30/67)	Not reported	
Ages 12-17 yrs:			
Normal, % (n/N)	65 (26/40)	Not reported	
Abnormal, % (n/N)	35 (14/40)	Not reported	
METAVIR fibrosis score [a], overall:			
F0, % (n/N)	12.5 (13/107)	Not reported	
F1, % (n/N)	82.2 (88/107) [b]	Not reported	
F2, % (n/N)	1.9 (2/107)	Not reported	
F3, % (n/N)	1 (1/107)	Not reported	
Ages 3-11 yrs:			
F0, % (n/N)	13.8 (9/67)	Not reported	
F1, % (n/N)	83.1 (56/67)	Not reported	
F2, % (n/N)	1.5 (1/67)	Not reported	
F3, % (n/N)	1.5 (1/67)	Not reported	
Ages 12-17 yrs:			
F0, % (n/N)	10.3 (4/40)	Not reported	
F1, % (n/N)	87.2 (35/40)	Not reported	
F2, % (n/N)	2.6 (1/40)	Not reported	
F3, % (n/N)	0 (0/40)	Not reported	
METAVIR inflammatory activity score, overall:			
None, % (n/N)	6 (6/107)	Not reported	
Mild, % (n/N)	44 (47/107)	Not reported	
Moderate, % (n/N)	30 (32/107)	Not reported	
Severe, % (n/N)	18 (19/107)	Not reported	
Missing, % (n/N)	3 (3/107)	Not reported	
Ages 3-11 yrs:			
None, % (n/N)	4 (3/67)	Not reported	
Mild, % (n/N)	40 (27/67)	Not reported	
Moderate, % (n/N)	33 (22/67)	Not reported	
Severe, % (n/N)	19 (13/67)	Not reported	
Missing, % (n/N)	3 (2/67)	Not reported	
Ages 12-17 yrs:			
None, % (n/N)	8 (3/40)	Not reported	
Mild, % (n/N)	50 (20/40)	Not reported	
Moderate, % (n/N)	25 (10/40)	Not reported	
Severe, % (n/N)	15 (6/40)	Not reported	
Missing, % (n/N)	3 (1/40)	Not reported	
Liver steatosis, % (n/N), overall			
0	71 (76/107)	Not reported	
> 0 to ≤ 5%	22 (24/107)	Not reported	
>5% to ≤ 32%	4 (4/107)	Not reported	
Missing	3 (3/107)	Not reported	
Ages 3-11 yrs:			
0	69 (46/67)	Not reported	
> 0 to ≤ 5%	24 (16/67)	Not reported	
>5% to ≤ 32%	4 (3/67)	Not reported	
Missing	3 (2/67)	Not reported	
Ages 12-17 yrs:			
0	75 (30/40)	Not reported	

> 0 to ≤ 5%	20 (8/40)	Not reported	
>5% to ≤ 32%	3 (1/40)	Not reported	
Missing	3 (1/40)	Not reported	

Notes/comments:
[a] METAVIR fibrosis scores: F0=no fibrosis; F1=portal fibrosis without septa; F2=portal fibrosis with few septa; F3=septal fibrosis without cirrhosis; F4=cirrhosis
[b] Percentage incorrectly reported as 84.6; corrected by reviewer

Outcomes	**Baseline**	**Post-treatment**	**p-value**
Viral Response, % (n/N)			
RVR (4 wk):	n/a	Not reported	
EVR (12 wk) by genotype, % (n/N): [c]			
Overall population (n=107)	n/a	68 (73/107)	
Genotype 1 (n=72)	n/a	60 (43/72)	
Genotypes 2 & 3 (n=30)	n/a	87 (26/30)	
Genotype 4 (n=5)	n/a	80 (4/5)	
EOT (End of treatment) by genotype, % (n/N) : [c]			
Overall population (n=107)	n/a	70 (75/107)	
Genotype 1 (n=72)	n/a	60 (43/72)	
Genotypes 2 & 3 (n=30)	n/a	93 (28/30)	
Genotype 4 (n=5)	n/a	80 (4/5)	
SVR (End of follow-up), % (n/N):	n/a	65 (70/107)	

Notes/comments:
Stated that all genotype 3 patients with high viral load (n=9) attained SVR, although 8/9 had received only 24 weeks of treatment (which was contrary to the protocol-specified treatment duration)
[c] EVR and EOT were not reported for the overall population but calculated by reviewer from percentages

SVR subgroup data, % - reported for genotype 1 only (n=72):			
Patients with RVR achieving SVR	n/a	89	
Patients with EVR achieving SVR	n/a	84	
SVR by genotype, % (n/N):			p=0.0005 but not stated which comparison this refers to
Genotype 1	n/a	53 (38/72)	
Genotype 2/3	n/a	93 (28/30)	
Genotype 4	n/a	80 (4/5)	
SVR by genotype and baseline viral load, % (n/N)			
Genotype 1 (n=72):			
Low (≤600,000 IU/mL)	n/a	72 (28/39)	p=0.0006
High (>600,000 IU/mL)	n/a	29 (9/31)	(low vs high)
Missing	n/a	50 (1/2)	
Genotypes 2 & 3 (n=30):			
Low (≤600,000 IU/mL)	n/a	94 (15/16)	
High (>600,000 IU/mL)	n/a	100 (13/13)	
Missing	n/a	0 (0/1)	
Genotype 4 (n=5):			
Low (≤600,000 IU/mL)	n/a	100 (3/3)	
High (>600,000 IU/mL)	n/a	0 (0/1)	
Missing	n/a	100 (1/1)	
Other viral response outcomes: [b]			
SVR by genotype and age group, % (n/N)			

Genotype 1 (n=72):			
Ages 3-11 yrs	n/a	51 (24/47)	
Ages 12-17 yrs	n/a	56 (14/25)	
Genotypes 2 & 3 (n=30):			
Ages 3-11 yrs	n/a	88 (14/16)	
Ages 12-17 yrs	n/a	100 (14/14)	
Genotype 4 (n=5):			
Ages 3-11 yrs	n/a	75 (3/4)	
Ages 12-17 yrs	n/a	100 (1/1)	
SVR by genotype and mode of infection, % (n/N)			
Genotype 1 (n=72):			
Vertical	n/a	50 (26/52)	
Transfusion/parenteral	n/a	80 (4/5)	
Sporadic/other (not specified)	n/a	53 (8/15)	
Genotypes 2 & 3 (n=30):			
Vertical	n/a	95 (18/19)	
Transfusion/parenteral	n/a	100 (6/6)	
Sporadic/other (not specified)	n/a	80 (4/5)	
Genotype 4 (n=5):			
Vertical	n/a	75 (3/4)	
Transfusion/parenteral	n/a	100 (1/1)	
Sporadic/other (not specified)	n/a	n/a	
SVR by genotype and baseline ALT, % (n/N) [c]			
Genotype 1 (n=72):			
Normal	n/a	56 (23/41)	
Abnormal	n/a	48 (15/31)	
Genotypes 2 & 3 (n=30):			
Normal	n/a	90 (18/20)	
Abnormal	n/a	100 (10/10)	
Genotype 4 (n=5):			
Normal	n/a	50 (1/2)	
Abnormal	n/a	100 (3/3)	
Non-response, % (n/N):	n/a	Not reported	
Relapse, by genotype, % Genotype 1	n/a	12% (9/72) G1 cohort thus 8% (9/107) whole cohort	
Genotype 2	n/a	0	
Genotype 3	n/a	0	
Genotype 4	n/a	0	
Notes/comments: [b] SVR was also reported by genotype-and-sex subgroups (data not extracted) [c] Stated that normalisation of ALT occurred in 34 of 44 patients (77%) who had elevated ALT at baseline; in most (27/34) of these patients (79%) biochemical response was associated with SVR			
Quality of life outcomes	Not reported	Not reported	
Adverse Events (AE)			
Dose discontinuation for AE, % (n/N): Thrombocytopenia (week 42)	n/a	1 (1/107) [d]	
Other reason	n/a	0 (0/107)	

Dose reduction for AE, % (n/N):			
Any adverse event, overall	n/a	25 (27/107)	
Ages 3-11 yrs	n/a	19 (13/67)	
Ages 12-17 yrs	n/a	35 (14/40)	
Blood & lymphatic disorders, overall	n/a	17 (18/107)	
Ages 3-11 yrs	n/a	9 (6/67)	
Ages 12-17 yrs	n/a	30 (12/40)	
Anaemia, overall	n/a	7 (8/107) [e]	
Ages 3-11 yrs	n/a	4 (3/67)	
Ages 12-17 yrs	n/a	10 (4/40)	
Neutropenia, overall	n/a	12 (13/107)	
Ages 3-11 yrs	n/a	6 (4/67)	
Ages 12-17 yrs	n/a	23 (9/40)	
Gastrointestinal disorders, overall	n/a	2 (2/107)	
Ages 3-11 yrs	n/a	3 (2/67)	
Ages 12-17 yrs	n/a	0 (0/40)	
Diarrhoea, overall	n/a	1 (1/107)	
Ages 3-11 yrs	n/a	1 (1/67)	
Ages 12-17 yrs	n/a	0 (0/40)	
Nausea, overall	n/a	2 (2/107)	
Ages 3-11 yrs	n/a	3 (2/67)	
Ages 12-17 yrs	n/a	0 (0/40)	
Vomiting, overall	n/a	1 (1/107)	
Ages 3-11 yrs	n/a	1 (1/67)	
Ages 12-17 yrs	n/a	0 (0/40)	
Fall, overall	n/a	1 (1/107)	
Ages 3-11 yrs	n/a	0 (0/67)	
Ages 12-17 yrs	n/a	3 (1/40)	
Weight/growth decrease, overall [f]	n/a	10 (11/107)	
Ages 3-11 yrs	n/a	9 (6/67)	
Ages 12-17 yrs	n/a	13 (5/40)	
Pruritic rash, overall	n/a	1 (1/107)	
Ages 3-11 yrs	n/a	0 (0/67)	
Ages 12-17 yrs	n/a	3 (1/40)	
Specific AE of ≥10% incidence, % (n/N) [g]			
Any treatment-related AE	n/a	100 (107/107) [h]	
Anaemia, overall	n/a	11 (12/107)	
Ages 3-11 yrs	n/a	6 (4/67)	
Ages 12-17 yrs	n/a	20 (8/40)	
Leukopenia, overall	n/a	10 (11/107)	
Ages 3-11 yrs	n/a	11 (7/65) [i]	
Ages 12-17 yrs	n/a	10 (4/40)	
Neutropenia, overall	n/a	33 (35/107)	
Ages 3-11 yrs	n/a	24 (16/67)	
Ages 12-17 yrs	n/a	48 (19/40)	
Abdominal pain	n/a	21 (22/107)	
Ages 3-11 yrs	n/a	25 (17/67)	
Ages 12-17 yrs	n/a	13 (5/40)	
Upper gastrointestinal disorder	n/a	12 (13/107)	
Ages 3-11 yrs	n/a	9 (6/67)	
Ages 12-17 yrs	n/a	18 (7/40)	
Nausea	n/a	18 (19/107)	

Ages 3-11 yrs	n/a	18 (12/67)	
Ages 12-17 yrs	n/a	18 (7/40)	
Vomiting	n/a	27 (29/107)	
Ages 3-11 yrs	n/a	40 (27/67)	
Ages 12-17 yrs	n/a	5 (2/40)	
Aesthenia	n/a	15 (16/107)	
Ages 3-11 yrs	n/a	16 (11/67)	
Ages 12-17 yrs	n/a	13 (5/40)	
Chills	n/a	21 (23/107)	
Ages 3-11 yrs	n/a	27 (18/67)	
Ages 12-17 yrs	n/a	13 (5/40)	
Fatigue	n/a	30 (32/107)	
Ages 3-11 yrs	n/a	33 (22/67)	
Ages 12-17 yrs	n/a	25 (10/40)	
Injection site erythema	n/a	29 (31/107)	
Ages 3-11 yrs	n/a	27 (18/67)	
Ages 12-17 yrs	n/a	33 (13/40)	
Irritability	n/a	14 (15/107)	
Ages 3-11 yrs	n/a	15 (10/67)	
Ages 12-17 yrs	n/a	13 (5/40)	
Fever	n/a	80 (86/107)	
Ages 3-11 yrs	n/a	90 (60/67)	
Ages 12-17 yrs	n/a	65 (26/40)	
Weight decrease	n/a	19 (20/107)	
Ages 3-11 yrs	n/a	21 (14/67)	
Ages 12-17 yrs	n/a	15 (6/40)	
Anorexia	n/a	29 (31/107)	
Ages 3-11 yrs	n/a	37 (25/67)	
Ages 12-17 yrs	n/a	15 (6/40)	
Decreased appetite	n/a	22 (24/107)	
Ages 3-11 yrs	n/a	27 (18/67)	
Ages 12-17 yrs	n/a	15 (6/40)	
Arthralgia	n/a	17 (18/107)	
Ages 3-11 yrs	n/a	21 (14/67)	
Ages 12-17 yrs	n/a	10 (4)	
Myalgia	n/a	17 (18/107)	
Ages 3-11 yrs	n/a	21 (14/67)	
Ages 12-17 yrs	n/a	10 (4)	
Dizziness	n/a	14 (15/107)	
Ages 3-11 yrs	n/a	13 (9/67)	
Ages 12-17 yrs	n/a	15 (6/40)	
Headache	n/a	62 (66/107)	
Ages 3-11 yrs	n/a	66 (44/67)	
Ages 12-17 yrs	n/a	55 (22/40)	
Alopecia	n/a	17 (18/107)	
Ages 3-11 yrs	n/a	18 (12/67)	
Ages 12-17 yrs	n/a	15 (6/40)	
Psychiatric or behavioural AE, %:	n/a	28	
Specific psychiatric/behavioural AE reported by at least 2 patients, %: [j]			
Nervousness	n/a	8	
Agitation	n/a	4	
Aggression	n/a	3	

Mood alteration	n/a	3	
Anxiety	n/a	3	
Insomnia	n/a	3	
Restlessness	n/a	3	
Anger	n/a	2	
Depression	n/a	2	
Depressed mood	n/a	2	
Affect lability	n/a	2	
Clinical laboratory AE, % (n/N):			
≥1 abnormal thyroid stimulating hormone value during treatment or follow up	n/a	23 (25/107)	
Clinical hypothyroidism	n/a	3 (3/107)	
Mortality, % (n/N)	n/a	0 (0/107)	
Effects on growth Clearly inhibited growth velocity <3rd percentile during treatment phase, % (n/N)	n/a	70 (75/107)	
Growth velocity, cm/yr			
Treatment period	n/a	2.47 ± 2.22	
Follow-up period	n/a	5.73 ± 4.1	
Mean (SD) height percentile, overall	50.87 (28.89)	44.25 (27.59) [k]	
Ages 3-11 yrs	51.14 (28.07)	42.32 (25.82) [k]	
Ages 12-17 yrs	50.41 (30.57)	47.49 (30.39) [k]	
Mean change in height percentile:			
Baseline to end of treatment	n/a	-7.7	
During follow-up	n/a	1.1	
Mean (SD) weight percentile, overall	56.57 (29.35)	53.39 (29.51) [k]	
Ages 3-11 yrs	54.84 (30.3)	50.46 (30.33) [k]	
Ages 12-17 yrs	59.47 (27.82)	58.3 (27.76) [k]	
Mean change in weight percentile:			
Baseline to end of treatment	n/a	-15.5	
During follow-up	n/a	12.3	

Notes/comments:

[d] The patient who discontinued due to thrombocytopenia attained SVR

[e] The number of patients who had dose reduction due to anaemia was stated as both 7 (Table 4) and 8 (text, page 504)

[f] Stated that dose adjustment was recommended when weight change was ≥10% for ribavirin and if body surface area changed ≥10% for PEG IFN α-2b (meaning appears ambiguous)

[g] Stated that no treatment-related serious AE were reported, no patients developed diabetes and no patients had life-threatening AE

[h] Stated that most treatment-related AE were consistent with flu-like symptoms such as fever, headache and fatigue

[i] Rounding error in percentage corrected by reviewer

[j] Stated that the psychiatric/behavioural AE were mild or moderate in severity and did not require dose reduction, treatment discontinuation, or antidepressant therapy

[k] Data are for end of follow-up. Stated that the decrease in mean height percentile during treatment was greater in patients whose treatment duration was longer (n=55, mean 334 days) than in those whose treatment duration was shorter (n=52, mean 155 days; -11.8 vs -3.6 respectively)

Methodological comments: Note if n/a.

Allocation to treatment groups: n/a

Allocation concealment: n/a

Blinding: None (stated open label)

Analysis by intention to treat: n/a
Comparability of treatment groups at baseline: n/a
Method of data analysis: Statistical tests and comparisons not reported. Stated that carry-forward analysis was performed which included patients who had missing HCV RNA data at 24 weeks after treatment but undetectable HCV RNA at 12 weeks after treatment as sustained responders
Sample size/power analysis: Not reported
Attrition/drop-out: Reported with reasons

General comments
Generalisability: Treatment-naïve patients of white ethnicity with body weight not exceeding 90kg, with evidence of fibrosis, inflammation and/or elevated ALT but without concurrent HBV or HIV infection
Inter-centre variability: Not reported other than the numbers of patients recruited at each of the 22 centres (in supplementary online material)
Conflict of interests: All but one of the 32 authors received funding from or were employed by the drug manufacturer (Schering-Plough); the drug manufacturer also supported writing of the manuscript
Other: Note that 8 of 9 genotype 3 patients with high viral load received only 24 weeks of therapy, in contrast to the 48 weeks specified in the protocol for this group

Quality criteria for assessment of uncontrolled, single cohort studies

1. Were the patient selection criteria specified *a priori*?	Yes
2. Was the participant blinded to treatment	N/a (stated open label)
3. Is there any evidence to suggest that the authors measured more outcomes than they reported?	Unclear
4. Were withdrawals and dropouts completely described?	Yes
5. i) Did the analysis account for missing data? ii) If so, were the methods appropriate?	Unclear (no formal analysis reported)

Studies of peginterferon α-2b: Ghaffar and colleagues (2009)[47]

Reference and Design	Intervention	Participants	Outcome measures
Ref ID: #115 **Author:** Ghaffar *et al*.[47] **Year:** 2009 **Study design**: Single cohort study **Number of centres:** 1 **Country**: Egypt **Funding**: stated by donations	**Group 1:** n = 7 **Drug 1:** PEG IFN α-2b *Dose*: 1.5 µg/kg once per week *Duration*: 52 weeks **Drug 2:** Ribavarin *Dose*: 15mg/kg daily in 2 doses *Duration*: as above **Study design details:** Very little aggregate data presented, is a case series in effect.	**Total numbers involved**: 7 **Treatment naïve:** not reported for 6 patients **Previous treatment:** 1, IFN **HCV/HIV co-infection:** not reported **Duration of infection:** unclear (4.5 years for two, 12.7 years for remaining five) **Inclusion criteria**: aged between 8 and 16 years, both genders, chronic HCV infection (positive antibodies with HCV-RNA positivity and ALT/AST ≤ 1.5 times upper limit of normal), well compensated liver disease, normal levels for haemoglobin, platelets, white blood cells, glucose, serum creatinine, normal thyroid profile and negative autoantibodies (anti-smooth muscle, antinuclear and anti-LKM). No co-infection with any other hepatotrophic virus or HIV. **Exclusion criteria:** not stated **Age (yrs), mean (±SD or range)**: mean not provided, ranged from 8-13, median 10 years (calculated by reviewer). **Gender male, n (%)**: 5 (71%) **Weight/BMI:** not reported **Ethnic groups, n (%)**: not reported **Mode of infection, n (%)**: Vertical: 1 (14%) Parenteral: 5 (author definition) (71%) Transfusion: 0 (unless included above) Vertical and parenteral: 1 (14%) **Genotypes, n (%)**: 4a: 1 (14%) 4b: 5 (71%) Not tested: 1 (14%) **Sample attrition/dropout**: not stated, assumed none	**Primary outcomes**: not stated as primary or secondary: SVR, EVR (not specifically defined), ETR, serum HCV-RNA, biochemical response (ALT, AST), side effects, bilirubin, blood count. **Secondary outcomes**: See above **Length of follow up**: 12 months after stopping treatment **Methods of assessing outcomes:** serum HCV-RNA was determined by Amplicor polymerase chain reaction, Roche diagnostics. Genotype subtypes determined by restriction fragment length polymorphism. ETR was defined as undetectable HCV-RNA at the end of treatment. SVR defined as undetectable HCV-RNA that persists during the entire 12 months post therapy. Histology: Classification system used: modified Knodell-Ishak score

Definitions/comments:
Hepatomegaly reported as mild in 4 and negative in 3. Splenomegaly reported as mild in 4 and negative in 3

Participant characteristics /outcomes	Baseline	Post-treatment (wk 52)	
HCV RNA (IU/ml)	Median: 145.000	Low viremia, n=4	

	Range 74.000-758.000	Det[a], n=3	
Serum ALT (IU/L)	Median: 77 Range: 52-223	Median: 39 Range: 17-63	
Serum AST (IU/L)	Median:76 Range: 63-321	Median: 38 Range: 20-69	
Fibrosis score, mean (±SD):	See below for 4 participants[b]	See below for 4 participants[b]	
Necroinflammatory score, mean (±SD):	Not reported	Not reported	
Notes/comments: No mean or SD baseline characteristics reported. Median and range calculated by reviewer. [a]meaning of 'det' unclear [b]states HAI (?Histologic activity index) from liver biopsy showed improvement in 3 patients and fibrosis regression was seen in 1. Details of changes in scores for these 4 participants are reported only (4/18 became 3/18; 4/18 became 2/18, 5/18 became 2/18; and Fibrosis regression changed from 3/4 to 2/4).			
Outcomes	**Baseline**	**Post-treatment**	**p-value**
Viral Response, % (n/N) RVR (4 wk):			
EVR[c] (12 wk):		28.6% (2/7)	
ETR (52 weeks):	n/a	42.9% (3/7)	n/a
SVR (End of follow-up):	n/a	28.6% (2/7)	n/a
Notes/comments: States no differences between children with SVR and the rest of the group with regarding pretreatment biochemical or histological parameters, viral load, viral subtype nor mode of infection, but numbers too small to statistically compare. The two participants with SVR were the youngest of the group, both were infected parenterally, and the duration of HCV infection was shorter. [c]Not defined by study authors as EVR, but provides the proportion with undetectable HCV at 12 weeks and therefore classified as such by reviewer.			
SVR subgroup data, % (n/N):	n/a	Not reported	
Other viral response outcomes:	n/a	Not reported	
Non-response, % (n/N):	n/a	Not reported	
Relapse, % (n/N):	n/a	Not reported	
Notes/comments:			
Quality of life outcomes	n/a	Not reported	
Adverse Events, % (n/N) Dose discontinuation for any AE	n/a	Not reported	
Dose discontinuation for other reason	n/a	Not reported	
Dose reduction for any AE	n/a	0	
Dose reduction for anaemia	n/a	Not reported	
Dose reduction for neutropenia	n/a	Not reported	
Dose reduction for other	n/a	Not reported	
Specific adverse events, % (n/N) Flu like symptoms Excessive hair loss Mild reduction in blood counts Behavioural change	n/a	 100% (7/7) 14% (1/7) 14% (1/7) 14% (1/7)	
Mortality, % (n/N)	n/a	Not reported	
Effects on growth	n/a	Not reported	
Methodological comments: *Allocation to treatment groups:* n/a *Allocation concealment*: n/a *Blinding*: stated is an open labelled study *Analysis by intention to treat:* n/a *Comparability of treatment groups at baseline:* n/a *Method of data analysis:* no aggregate data presented and no statistical analyses undertaken			

Sample size/power analysis: n/a
Attrition/drop-out: not reported

General comments
Generalisability: minimal data provided on patient demographics, study undertaken in Egypt may limit generalisability to UK
*Inter-centre variability:*n/a
Conflict of interests: stated none declared

Quality criteria for assessment of uncontrolled, single cohort studies

1. Were the patient selection criteria specified *a priori*?	Yes
2. Was the participant blinded to the research question?	N/a
3. Is there any evidence to suggest that the authors measured more outcomes than they reported?	Unclear
4. Were withdrawals and dropouts completely described?	Not reported
5. i) Did the analysis account for missing data? ii) If so, were the methods appropriate?	Not applicable (no analysis)

Studies of peginterferon α-2b: Jara and colleagues (2008)[48]

Reference and Design	Intervention	Participants	Outcome measures
Ref ID: #168 **Author:** Jara *et al*.[48] **Year:** 2008 **Study design**: Single Cohort study (pilot study) **Number of centres:** 1 **Country**: Spain **Funding**: Not stated but Schering-Plough helped design the study and provided the treatments free of charge	**Drug 1:** PEG IFN α-2b subcutaneous *Dose*: 1.0µg/kg/wk *Duration*: 24 weeks genotype 2/3, 48 weeks genotype 1/4 **Drug 2: Ribavarin** *Dose*: 15mg/kg/d orally in 2 divided doses *Duration*: as above Discontinuation: Treatment discontinuation was considered at week 24 if serum HCV RNA titers remained detectable. In practice therapy was maintained even if no viral clearance, provided drugs were tolerated. Adjustments: PEG-IFN-α2b dose transiently decreased in those with a neutrophil count <1.25 x 10^9 cells/ml to avoid neutropenia. PEG-IFN-α2b temporarily discontinued if neutrophil counts fell below 1.00 x 10^9 cells/mL and resumed once neutrophil counts exceeded 1.00 x 10^9 cells/mL. Concurrent treatment: Oral vitamin E supplements. **Study design details:** two subgroups according to genotype and therefore duration of treatment (as above)	**Total numbers involved**: 30 (subgroup genotype 1,4 n=27; genotype 3 n=3) **Treatment naïve:** 24 (80%) **Previous treatment:** 6 (20%) treated with IFN-α monotherapy 3-5 years earlier. **HCV/HIV co-infection:** n/a **Duration of infection:** not stated **Inclusion criteria**: aged between 3 and 16 years and chronic hepatitis C, defined serum HCV RNA titers (>50 IU/ml) for ≥ 3 years with continuous or intermittently elevated ALT values. Non responders to IFN-α monotherapy eligible if they accounted for < than 25% of the patient population. **Exclusion criteria:** neutropenia (<1000 x 10^9 cells/L), anaemia (haemoglobin <10g/dL), thrombocytopenia (<150 x 10^9 cells/L), or decompensated liver disease. HIV and non-HCV liver disease. Comorbid medical conditions (eg moderate or severe depression, psychiatric conditions, seizures, renal insufficiency) that could compromise tolerability of the study drugs. Those testing positive for autoimmunity markers (antinuclear antibody, smooth muscle antibody, liver-kidney microsomal antibody type 1) enrolled if other features did not suggest autoimmune hepatitis. **Age (yrs), mean (±SD or range)**: 10 (range 3.5-16) **Gender male, n (%)**:: not stated **Weight, kg**: assumed median 36 (range 13-67) **Ethnic groups, n (%)**: not stated **Mode of infection, n (%)**: Vertical: 21 (70) Parenteral: 9 (30) **Genotypes, n (%)**: 1: 26 (87) 2: 0 3: 3 (10) 4: 1 (3)	**Primary outcomes**: SVR **Secondary outcomes**: RVR (not specifically defined), EVR (not specifically defined), virological response, predictors for SVR (not data extracted except previous treatment status), safety (adverse events), QoL & growth (very briefly in text) **Length of follow up**: followed up every 12 weeks for at least 24 weeks after the end of treatment. **Methods of assessing outcomes:** SVR defined as undetectable HCV RNA 24 weeks after treatment cessation. HCV RNA titers were measured with use of a polymerase chain reaction assay every month during the first 24 weeks of therapy, at 4- to 12-week intervals until completion of therapy, at end of treatment, and each follow-up visit. Qualitative (Cobas Amplicor HCV Monitor 2.0; Roche Diagnostics; Basel, Switzerland: lower limit of detection ≥50 IU/mL) and quantitative (Cobas Amplicor HCV Monitor 2.0; lower limit of detection ≥600 IU/mL) analyses performed. Histology: Knodell

		Sample attrition/dropout: 2 discontinued in the 48 week treatment group before 24 weeks (1 hyperthyroidism, 1 high-grade fever). 5 discontinued between 24-48 weeks of treatment (2: lack of response; 2 breakthrough; 1 hyperthyroidism) [a]data from 29 who gave consent for liver biopsy	score 3 (range 1-8)[a] Classification system used: Knodell scoring system Safety assessed by clinical visits and laboratory tests, weekly for 4-weeks, then monthly until week 24, then 4- to 12-week intervals until completion of therapy. Hospital admission for 48 hours after first administration to monitor reactions to therapy.

Definitions/comments: 6 had underlying disease (clotting factor X deficiency, n=1; agammaglobulinemia, n=1; acute lymphocytic leukaemia, n=1; cardiomyopathy, n=3)
Mean duration of liver dysfunction was 5 (range 1.2-11.1) years

Participant characteristics /outcomes	**Baseline**	**Post-treatment**	
HCV RNA (IU/ml), log_{10} mean (range)	5 (3-6) [b]	Not reported	
Serum ALT (IU/L), mean (range):	75 (29-232)[c]	Not reported	
Serum AST (IU/L), mean (range):	52 (24-157)	Not reported	
Fibrosis score **<4** **4-7** **≥ 8**	 58% 31% 10%	 Not reported Not reported Not reported	
Cirrhosis	0%	Not reported	
Necroinflammatory score, mean (±SD):	Not reported	Not reported	

Notes/comments: Also reports autoimmune markers (antinuclear antibody; smooth muscle antibody; liver-kidney microsomal antibody type 1) and viral load of 10^5 x IU/ml. In 20 patients (66%) with only 1 participant having log_{10} viral load <4.5.
[b]Quantitative tests indicated a viral load of $>10^5$ x IU/mL (reviewer note - should this be 5 x10^5?) in 20/30 patients (67%) with only 1 patient having log_{10} viral load <4.5.
[c]States that all but 2 patients (i.e. 28/30) had elevated ALT values at baseline.

Outcomes	**Baseline**	**Post-treatment**	**p-value**
Viral Response, % (n/N) RVR[c] (4 wk):	 n/a	 3% (1/30)	
EVR[d] (12 wk):	n/a	52% (15/29)	
Virological response[e] (wk 24):	n/a	64% (18/28)	
SVR (End of follow-up):	n/a	50% (15/30)	n/a

Notes/comments: all who attained SVR remained HCV RNA negative at further follow-up visits (up to 36 months) and had normal liver function. Of those who had a virological response at week 24 (n=18), 3 had genotype 3 and 15 had genotype 1 or 4. Also stated ALT values normalised in 14/15 children who attained an SVR during the first month and remained normal throughout. One patient had abnormal ALT values during therapy, but ALT titers returned to normal once therapy was stopped.
[c]Not defined by study authors as RVR, but provides the proportion with negative HCV RNA at 4 weeks and therefore classified as such by reviewer.
[d]Not defined by study authors as EVR, but provides the proportion with negative HCV RNA at 12 weeks and

therefore classified as such by reviewer. Proportion reported not calculated on total population. [e]Not defined by study authors as such, but provides the proportion with negative HCV RNA at 24 weeks and therefore classified as such by reviewer. Proportion reported not calculated on total population.			
SVR subgroup data, % (n/N): *SVR by genotype* Genotype 3 Genotype 1 Genotype 4	n/a	 100% (3/3) 46% (12/26) 0 (0/1)	n/a
SVR by previous treatment (n=26)[f] Treatment naïve Re-treated (non-response/relapse)	n/a	 55% (11/20) 17% (1/6)	n/a
Other: Of the 15 patients who were HCV RNA negative at week 24, 11 (73%) achieved an SVR. 1 participant in the genotype 1/4 group who discontinued therapy attained an SVR. 87% (13/15) who were HCV RNA negative at 12 weeks (reviewer classified as EVR) achieved an SVR; 14% (2/14) who were HCV RNA positive at 12 weeks achieved an SVR. [f]all genotype 1 patients, remaining 4 patients (3 x genotype 3, 1 x genotype 4) were not included.			
Non-response, % (n/N):	n/a	47% (14/30)	
Relapse, % (n/N):	n/a	3% (1/30)	
Notes/comments: Also reports virological status at week 12 for what is assumed by reviewer to be partial EVR (data not extracted).			
Quality of life outcomes	Not reported	Not reported	
Adverse Events, % (n/N) Dose discontinuation for any AE	 n/a	3 (1 high grade fever, 2 hyperthyroidism)	
Dose discontinuation for other reason	n/a	Not reported	
Dose reduction for any AE	n/a	Not reported	
Dose reduction for anaemia	n/a	0	
Dose reduction for neutropenia	n/a	23% (7/30)	
Dose reduction for other	n/a	Not reported	
Specific adverse events, % (n/N) Flu-like, drug related: -Fever -Fatigue -Myalgia -Abdominal pain -Nausea and vomiting -Headache Injection site: -Erythema Gastrointestinal: -Decreased appetite -Constipation Weight:[g] -Weight loss -Weight loss >5% baseline Behaviour/neurologic: -Irritability -Dizziness -Anxiety Hair, skin, mucosae, -Sore mouth -Hair loss -Nose bleeding -Dry skin -Pruritus		 100% (30/30) 73% (22/30) 33% (10/30) 43% (13/30) 27% (8/30) 67% (20/30) 33% (10/30) 77% (23/30) 10% (3/30) 67% (20/30) 23% (7/30) 33% (10/30)[h] 23% (7/30)[i] 7% (2/30) 43% (13/30) 10% (3/30) 10% (3/30) 10% (3/30) 7% (2/30)	

Endocrine: -Antithyroid antibodies -Hyperthyroidism -Transient high TSH or T4 Infections: -Upper respiratory tract -Gastrointestinal -Skin		 13% (4/30) 7% (2/30) 20% (6/30) 53% (16/30) 30% (9/30) 13% (4/30)	
Mortality, % (n/N)	n/a	Not reported	
Effects on growth, during 48 weeks Reduced by 1.6 cm compared with growth velocity 50th percentile for age and sex[j]		22/26 (3 fully grown)	
Notes/comments: TSH: thyroid-stimulating hormone; T4: thyroxine level [g] stated body weight had decreased by 4.8% by week 24 but returned to baseline values by week 48; [h]febrile hallucinations n=1; [i]complex migraine n=1; [j]stated growth velocity was entirely normal in the 6-month period after the end of treatment, however, the modest decrease in height percentile was not recovered.			
Methodological comments: *Allocation to treatment groups:* n/a *Allocation concealment*: n/a *Blinding*: n/a *Analysis by intention to treat:* n/a *Comparability of treatment groups at baseline:* n/a *Method of data analysis:* statistical analysis of relationships between patient baseline characteristics and SVR by Fisher exact tests, and patient baseline characteristics and responder status by Student's *t* test. *Sample size/power analysis:* stated was a pilot study *Attrition/drop-out:* numbers and reasons provided. **General comments** *Generalisability:* Limited data available on patient demographics, and small sample size with wide range of ages and mixture of routes of infection. Likely to be most generalisable to genotype 1 population. *Inter-centre variability: n/a* *Conflict of interests:* Not stated *Other:*			

Quality criteria for assessment of uncontrolled, single cohort studies

1. Were the patient selection criteria specified *a priori*?	Yes
2. Was the participant blinded to the research question?	N/a
3. Is there any evidence to suggest that the authors measured more outcomes than they reported?	Unclear
4. Were withdrawals and dropouts completely described?	Yes
5. i) Did the analysis account for missing data? ii) If so, were the methods appropriate?	No

Appendix 5 Table of excluded studies of clinical effectiveness

Retrieved references for screening that were excluded (n=45) (a=abstracts that appear to refer to the same study).

Reference	Full paper/abstract	Exclusion criterion
Abdel-Aziz DH, Sabry NA, El-Sayed MH, El-Gazayerly ON. Efficacy and safety of pegylated interferon in children and adolescents infected with chronic hepatitis C: a preliminary study. *Journal of Pharmacy Practice* 2011; 24(2):203-210.	paper	Outcome
Adiv OE, Zion N, Shaoul R. Pegylated Interferon and Ribavirin Treatment for Children with Hepatitis C. *Journal of Pediatric Gastroenterology and Nutrition* 2010; 50:E161.	abstract	Study design (retrospective)
Akram M, Idrees M, Zafar S, Hussain A, Butt S, Afzal S et al. Effects of host and virus related factors on interferon-alpha+ribavirin and pegylated-interferon + ribavirin treatment outcomes in chronic Hepatitis C patients. *Virology Journal* 2011; 8:234.	paper	Population (age)
Baker RD, Dee D, Baker SS. Response to pegylated interferon alpha-2b and ribavirin in children with chronic hepatitis C. *Journal of Clinical Gastroenterology* 2007; 41(1):111-114.	paper	Population (age)
Carey I, Pariante C, Bansal S, Subramaniam P, Tizzard S, Vergani D et al. Psychiatric side effects of antiviral therapy with Pegylated *interferon and ribavirin are associated with poor response* in children with chronic hepatitis C. *Gut* 2010; 59: A43-A44.	abstract a	Insufficient detail in abstract
Carey I, Tizzard S, Bansal S, Subramaniam P, Vergani D, Mieli-Vergani G. Response to pegylated interferon + ribavirin in children with chronic hepatitis c is associated with more severe haematological toxicity and fewer neuropsychiatric symptoms. Journal of *Pediatric Gastroenterology and Nutrition* 2010; 50(Suppl 2): E35-E36.	abstract a	Insufficient detail in abstract
Carey I, Bansal S, Mendes A, Subramaniam P, Cebecauerova D, Vergani D et al. Low pre-treatment numbers of CD4+/PD-1+ lymphocytes and low HCV-specific IL-10 production during therapy with pegylated-interferon+ribavirin predict response in children with chronic hepatitis C. Journal of Pediatric Gastroenterology and Nutrition 2010; 50(Suppl 2): E17.	abstract a	Insufficient detail in abstract
Carey I, Bruce MJ, Bansal S, Tizzard S, Mendes A, Joshi D et al. Genetic, Virological and Immunological Pre-Treatment Predictors of Therapy Response to Peg-Ifn/Ribavirin in Children with Chronic Hepatitis C. *Hepatology* 2011; 54:469A-470A.	abstract	Insufficient detail in abstract
Carey I, Mendes A, Cebecauerova D, Bansal S,	abstract a	Insufficient detail in

Subramaniam P, Tizzard S et al. Low Pre-Treatment Numbers of Cd4+/Pd1+Lymphocytes and Low Hcv-Specific Il-10 Production During Therapy with Pegylated-Interferon Plus Ribavirin Predict Response in Children with Chronic Hepatitis C. *Journal of Hepatology* 2010; 52:S266.		abstract
Carey I, Mendes A, Cebecauerova D, Bansal S, Subramaniam P, Tizzard S et al. Low Nk Cell Number, Low HCV-Specific Il-10 Production and High Cd56(Bright) Cell Number Predict Response to Pegylated-Interferon/Ribavirin Therapy in Chronic Hepatitis C in Children. *Journal of Hepatology* 2010; 52:S176-S177.	abstract a	Insufficient detail in abstract
Carey I, Mendes A, Bansal S, Subramaniam P, Longhi MS, Cebecauerova D et al. Sharp Decrease in HCV-Specific Interferon-Gamma and Il-10 Production During Antiviral Therapy with Pegylated Interferon and Ribavirin Predict Sustained Virological Response in Children with Chronic Hepatitis C. *Hepatology* 2009; 50(4):634A.	abstract a	Insufficient detail in abstract
Carey I, Cebecauerova D, Bansal S, Subra-Maniam P, Hussain MJ, Mytilinaiou M et al. Response to Pegylated Interferon/Ribavirin in Chronic Hepatitis C in Children Is Predicted by Pre-Treatment Number of Activated Natural Killer (Nk) Cells. *Hepatology* 2008; 48(4):321A.	abstract	Insufficient detail in abstract
Carey I, Mytilinaiou M, Hussain M, Bansal S, Subramaniam P, Horner M et al. HCV-specific production of IL-10 and IFN-gamma-inducible protein-10 (IP-10) levels predict treatment response to pegylated interferon and ribavirin in children with chronic hepatitis C infection. *Hepatology* 2007; 46(4):279A.	abstract	Insufficient detail in abstract
Dusheiko G, Danta M. Can Peg-IFN alpha-2a plus ribavirin be used to treat patients with chronic hepatitis C and normal alanine aminotransferase levels? *Nature Clinical Practice Gastroenterology & Hepatology* 2005; 2(3):130-131.	abstract	Population
Etani Y, Ida S. Peginterferon alpha-2a, ribavirin and fluvastatin combination therapy for chronic hepatitis C in children and adolescents. *Gastroenterology* 2011;5:S457.	abstract	Insufficient detail in abstract
Fattovich Ggf, Baroni GS, Pasino M, Pierantonelli I, Covolo L, Ieluzzi D et al. Post-load insulin resistance does not predict virological response to treatment of chronic hepatitis C patients without the metabolic syndrome. *Digestive and Liver Disease* 2012; 44(5):419-425.	paper	Population
Fransen van de Putte DE, Fischer K, Posthouwer D, Mauser-Bunschoten EP. The burden of HCV treatment in patients with inherited bleeding disorders. *Haemophilia* 2011; 17(5):791-799.	paper	Population
Fung J, Lai C-L, Hung I, Young J, Cheng C, Wong	paper	Population

D et al. Chronic hepatitis C virus genotype 6 infection: Response to pegylated interferon and ribavirin. *Journal of Infectious Diseases* 2008; 198(6):808-812.		
Garcia-Algar O, Garriga L, Molera C. Sustained Viral Response Hematological Markers During The Treatment of Chronic Hepatitis C Infection in Children. *Hepatitis Monthly* 2012; 12(9):1-2.	paper	Design
Gehring S, Kullmer U, Koeppelmann S, Gerner P, Wintermeyer P, Wirth S. Prevalence of autoantibodies and the risk of autoimmune thyroid disease in children with chronic hepatitis C virus infection treated with interferon-alpha. *World Journal of Gastroenterology* 2006; 12(36):5787-5792.	paper	Population
Goodman ZD, Makhlouf HR, Liu L, Balistreri W, Gonzalez-Peralta RP, Haber B et al. Pathology of chronic hepatitis C in children: liver biopsy findings in the Peds-C Trial. *Hepatology* 2008; 47(3):836-843.	paper	Intervention
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):345-351.	paper	Population
Gramenzi A, Cursaro C, Margotti M, Balsano C, Spaziani A, Anticoli S et al. Ketoprofen, peginterferon 2a and ribavirin for genotype 1 chronic hepatitis C: a phase II study. *World Journal of Gastroenterology* 2009; 15(47):5946-5952.	paper	Population
Hierro CL, Alvarez L, Andueza S, Gordo-Giralt R, Lledin D, Camarena C et al. Influence of IL28B gene polymorphisms on sustained response to peginterferon plus ribavirin in children with chronic hepatitis. *Journal of Hepatology* 2011; 54(Suppl 1): S524-S525.	abstract	Insufficient detail in abstract
Hoofnagle JH. Peds-C. Hepatology 2005; 41(3):421.	paper (1 pg)	Outcome
Inati A, Taher A, Ghorra S, Koussa S, Taha M, Aoun E et al. Efficacy and tolerability of peginterferon alpha-2a with or without ribavirin in thalassaemia major patients with chronic hepatitis C virus infection. *British Journal of Haematology* 2005; 130(4):644-646.	paper	Population
Inui A, Komatsu H, Sogo T, Hashimoto T, Fujisawa T. Pegylated interferon-alpha2b and ribavirin combination therapy for pediatric patients with chronic hepatitis C. *Acta Hepatologica Japonica* 2008; 49(8):386-388.	paper	Language
Jenke AC, Moser S, Orth V, Zilbauer M, Gerner P, Wirth S. Mutation frequency of NS5A in patients vertically infected with HCV genotype 1 predicts sustained virological response to peginterferon alfa-2b and ribavirin combination therapy. *Journal*	paper	Population

of Viral Hepatitis 2009; 16(12):853-859.		
Jonas MM, Balistreri W, Gonzalez-Peralta RP, Haber B, Lobritto S, Mohan P et al. Pegylated interferon for chronic hepatitis C in children affects growth and body composition: results from the pediatric study of hepatitis C (PEDS-C) trial. *Hepatology* 2012; 56(2):523-531.	paper	Intervention
Kowala-Piaskowska A, Mozer-Lisewska I, Figlerowicz M, Sluzewski W. Adverse effects during the treatment with pegylated interferon and ribavirin in children with chronic hepatitis C. *Pharmacoepidemiology & Drug Safety* 2007; 16(10):1095-1103.	paper	Population
Kowala-Piaskowska A, Sluzewski W, Figlerowicz M, Mozer-Lisewska I. Early virological response in children with chronic hepatitis C treated with pegylated interferon and ribavirin. *Infection* 2007; 35(3):175-179.	paper	Intervention
Kowala-Piaskowska A, Mozer-Lisewska I, Januszkiewicz-Lewandowska D, Michalak M, Zeromski J, Madalinski K et al. RNA-HCV viral load in serum, peripheral blood mononuclear cells and liver in children with chronic hepatitis C. *Acta Poloniae Pharmaceutica* 2012; 69(5):859-863.	paper	Intervention
Michielsen P, Bottieau E, Van VH, Van ME, Vandemaele E, Denys M et al. Treatment of chronic hepatitis C in patients with human immunodeficiency virus (HIV) with weekly peginterferon alpha-2b plus ribavirin: a multi-centred Belgian study. *Acta Gastroenterologica Belgica* 2009; 72(4):389-393.	paper	Population
Moghaddam MA, Zali MR, Andabili SHA, Derakhshan F, Miri SM, Alavian SM. High rate of virological response to peginterferon alpha-2a-ribavirin among non-cirrhotic Iranian hemophilia patients with chronic hepatitis C. *Iranian Red Crescent Medical Journal* 2012; 14(8):2.	paper	Population
Mohan N, Ganeja V, Kaul D, Khanna V. PEG interferon alpha 2a (40kD) plus ribavirin treatment in thalassemic children and adolescents with chronic hepatitis C. *Journal of Pediatric Gastroenterology and Nutrition* 2007; 44:144.	abstract	Insufficient detail in abstract
Nelson DR, Zeuzem S, Andreone P, Ferenci P, Herring R, Jensen DM et al. Balapiravir plus peginterferon alfa-2a (40KD)/ribavirin in a randomized trial of hepatitis C genotype 1 patients. *Annals of Hepatology* 2012; 11(1):15-31.	paper	Population
Osaki Y, Ueda Yyk, Marusawa H, Nakajima J, Kimura T, Kita R et al. Decrease in alpha-fetoprotein levels predicts reduced incidence of hepatocellular carcinoma in patients with hepatitis C virus infection receiving interferon therapy: a single center study. *Journal of Gastroenterology* 2012; 47(4):444-451.	paper	Population

Pawlowska M, Halota W. Pegylated Interferon Alpha-2a and Ribavirin in the Treatment of Children with Chronic Hepatitis C. *Gastroenterology* 2009; 136(5):A839.	abstract	Insufficient detail in abstract
Rodrigue JR, Balistreri W, Haber B, Jonas MM, Mohan P, Molleston JP et al. Impact of hepatitis C virus infection on children and their caregivers: quality of life, cognitive, and emotional outcomes. *Journal of Pediatric Gastroenterology & Nutrition* 2009; 48(3):341-347.	paper	Population
Sluzewski W, Kowala-Piaskowska A, Wysocki J, Figlerowicz M, Gorczyca A, Halota W et al. Treatment of chronic hepatitis C in children with pegylated interferon alpha2a and ribavirin--a multi-center study. *Acta Poloniae Pharmaceutica* 2012; 69(2):319-326.	paper	Population
Sokal E, Bourgois A, Stephenne X, Silveira T, Porta G, Gardovska D et al. Multicenter trial of peginterferon alfa-2A and ribavirin for paediatric chronic hepatitis C. *Journal of Pediatric Gastroenterology and Nutrition* 2009; 48(Suppl 3):E13.	abstract	Insufficient detail in abstract
Tabatabaei SV, Alavian SM, Behnava B, Keshvari M, Miri SM, Karimi EP et al. Anti-HCV treatment of thalassemia major adolescents with peginterferon alfa-2a and ribavirin. *Hepatology International* 2011 Hepatology International conference (source unclear).	abstract	Insufficient detail in abstract
Tabatabaei SV, Alavian SM, Keshvari M, Behnava B, Miri SM, Elizee PK et al. Low dose ribavirin for treatment of HCV infected thalassemia major patients; new indications for combination therapy. *Hepatitis Monthly* 2012; 12(6):372-381.	paper	Population
Wirth S, Pieper-Boustani H, Lang T, Ballauff A, Kullmer U, Gerner P et al. Peginterferon alfa-2b plus ribavirin treatment in children and adolescents with chronic hepatitis C. *Hepatology* 2005; 41(5):1013-1018.	paper	Population
Zhang H. Preliminary observational study on efficacy and tolerability of peg-IFN on 151 pediatric and adolescent chronic hepatitis C patients. Hepatology 2009; 50(Suppl 4):759A-760A.	abstract	Intervention

Appendix 6 Table of excluded studies for systematic review of health-related quality of life

Adults

Study	Reference	Reason for exclusion
Scalone	Scalone L, Ciampichini R, Fagiuoli S, Gardini I, Del PA, Gaeta L et al. Testing the performance of the newly developed version of the EQ-5D with 5 levels of severity: Application on a cohort of patients with chronic hepatic diseases. *Value in Health* 2010; Conference(var.pagings):7.	Abstract
Fagiouli	Fagiuoli S, Scalone L, Ciampichini R, Fusco F, Gaeta L, Del PA et al. Societal burden in patients with chronic hepatic diseases: The come study results. *Journal of Hepatology* 2012; Conference(var.pagings):S11-S12.	Abstract
Fagiouli	Fagiuoli S, Scalone L, Ciampichini R, Fusco F, Gaeta L, Del PA et al. Costs and Quality of life in patients with liver transplantation. *Liver Transplantation* 2012; Conference(var.pagings):S262.	Abstract
Fagouli	Fagiuoli S, Scalone L, Ciampichini R, Fusco F, Gaeta L, Del PA et al. Costs and quality of life in patients with chronic hepatic diseases: The COME study results. *Digestive and Liver Disease* 2012; Conference(var.pagings):S11.	Abstract
Bauch	Bauch PM, Sterling RK, Clement LM, Velez FF. Current evidence regarding the hepatitis C patient experience. *Value in Health* 2010; Conference(var.pagings):3-A75.	Abstract
John-Baptiste	John-Baptiste A, Tomlinson G, Hsu P, Krajden M, Heathcote J, Laporte A et al. Quality of life following antiviral therapy for chronic hepatitis C virus infection. Canadian Journal of Gastroenterology 2009; Conference(var.pagings).	Abstract
John-Baptiste	John-Baptiste AA, Tomlinson G, Hsu PC, Krajden M, Heathcote EJ, Laporte A et al. Sustained responders have better quality of life and productivity compared with treatment failures long after antiviral therapy for hepatitis C. American Journal of Gastroenterology 2009; 104:2439-2448.	Inappropriate QoL measure
Younossi	Younossi Z, Aggarwal J, Martin M, Hernandez N, Donepudi M, Bayliss M et al. Health-related quality-of-life among genotype 1 treatment-naive chronic Hepatitis C patients receiving telaprevir combination treatment: Post-hoc analyses of data from the advance trial. Journal of Hepatology 2012; Conference(var.pagings):S462-S463.	Abstract

Children

Study	Reference	Reason for exclusion
Akobeng	Akobeng AK, Davison S. Quality of life of patients with chronic hepatitis C virus infection. *Journal of Pediatric Gastroenterology and Nutrition* 2000; 30:224-226.	Inappropriate QoL measure
Hamer	Hamer C. The impact of combination therapy with peginterferon alpha-2a and ribavirin on the energy intake and body weight of adult hepatitis C patients. *Journal of Human Nutrition & Dietetics* 2008; 2:486-493.	Inappropriate QoL measure

Iorio	Iorio R, Pensati P, Botta S, Moschella S, Impagliazzo N, Vajro P et al. Side effects of alpha-interferon theraphy and impact on health-related quality of life in children with chronic viral hepatitis. *Pediatric Infectious Disease Journal* 1997; 16:984-990.	Inappropriate QoL measure
Rodrigue	Rodrigue JR, Balistreri W, Haber B, Jonas M, Mohan P, Molleston JP et al. Impact of hepatitis C virus (HCV) infection in children: Quality of life, emotional, and cognitive outcomes. *Hepatology* 2006; 44:437A-438A.	Abstract
Rodrigue	Rodrigue JR, Balistreri W, Haber B, Jonas MM, Mohan P, Molleston JP et al. Peginterferon with or without ribavirin has minimal effect on quality of life, behavioral/emotional, and cognitive outcomes in children. *Hepatology* 2011; 53:1468-1475.	Inappropriate QoL measure

Appendix 7 Health-related quality of life studies – data extraction forms

Reference (Lead author, year, ref id)

Bjornsson, 2009

Study Characteristics

Research question

What are the stated objectives of the study?

To determine the HRQoL in patients in different stages of hepatitis C virus and to compare HRQoL in HCV cirrhosis with non HCV induced cirrhosis.

Describe the type of study and study design.

Observational study comparing six cohorts with different stages of HCV or non HCV cirrhosis. Four are relevant to this review. Also included data from healthy controls.

Was the sample from i) the general population, ii) patients with the disease of interest, iii) individuals with knowledge of the disease, iv) other?

HCV patients attending regular follow-up in outpatient clinics in different centres.

What are the characteristics of the baseline cohort for the evaluation?

Indication / disease	Chronic hepatitis C[1]	Compensated cirrhosis[2]	Decompensated cirrhosis[3]	SVR[4]
Number	158	76	53	52
Age, median (IQR)	46 (13)	52 (11)	55 (10)	51 (14)
Sex, %	M 62%; F 38%	M 76%, F 24%	M 71%, F 29%	M 56%, F44%
	All patients			
QoL instrument	EQ-5D, SF-36			
Utility values, (Y/N)	Y			
Treatment effect, if reported	NA			

[1]defined as fibrosis stage 0-2
[2]defined ongoing HCV infection and histological signs of cirrhosis, or diagnosis of cirrhosis and no history of decompensation
[3]defined as ongoing HCV infection and non-HCV cirrhosis confirmed histologically or clinically, and a history of decompensation
[4]defined as having been treated with interferon and ribavirin and have negative HCV RNA 6 months post completion

Country/ setting

What is the country and setting for the evaluation?

Sweden, outpatient centres (16 clinics in 9 centres)

Data Sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review / synthesis or combination of previous studies, expert opinion?

Single observational study

Results

Summarise the results

EQ-5D index: CHC 0.811 (SD 0.230), compensated cirrhosis 0.749 (SD 0.212), Decompensated cirrhosis 0.656 (SD 0.266), SVR 0.792 (SD 0.209), healthy controls 0.819 (SD 0.217). SF-36 scores presented but not extracted as not relevant to the present economic model.

Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

Yes

Mapping

If a model was used, describe the type of model (eg. regression) or other conversion algorithm

NA

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

Impairment in HRQoL in patients with HCV was associated with the severity of liver disease, patients with decompensated cirrhosis exhibiting the highest impairment in HRQoL.

What are the implications of the study for the model

The data provide an alternative source for the HRQoL parameters in the model.

Reference (Lead author, year, refid)

Chong, 2003,

Study Characteristics

Research question

What are the stated objectives of the study?

To elicit utilities directly from those infected with HCV along the entire clinical spectrum of the disease (see below for details of categories).

Describe the type of study and study design.

Observational cohort study.

Was the sample from i) the general population, ii) patients with the disease of interest, iii) individuals with knowledge of the disease, iv) other?

People with HCV attending an outpatient clinic.

What are the characteristics of the baseline cohort for the evaluation?

Disease stage	No biopsy[a]	Mild/moderate HCV[b]	Compensated cirrhosis[c]	Decompensated cirrhosis[d]	HCC[e]	Transplant	SVR[f]
Number	35	44	24	9	15	30	36
Age, mean (SE)	47 (2.1)	44 (1.5)	57 (2.0)	57 (3.9)	63 (2.7)	54 (1.7)	48 (1.3)
Sex, n(%)[1]	M: 18 (51) F: 17 (49)	M: 32 (73) F: 12 (27)	M: 7 (29) F: 17 (71)[2]	M: 6 (67) F: 3 (33)	M: 14 (93) F: 1 (7)	M: 21 (70) F: 9 (30)	M: 23 (64) F: 13 (36)
Ethnicity, White, n(%)[1]	26 (74)	37 (84)	20 (83)	5 (55)	7 (47)	24 (80)	29 (81)
QoL instrument	Visual analogue scale (VAS); Standard Gamble (SG); Health Utility Index (HUI); EuroQol Index (EQ-5D). Only EQ-5D data extracted here as of relevance to economic model.						
Utility values, (Y/N)	Y						
Treatment effect	N/A						

[1] percentages for gender and ethnicity white have been calculated by reviewer on the basis of the intention to treat population. The study reports percentages based on the number of respondents to each question.
[2]Possible typographical error in the study report, this may be M: 17, F: 7.
[a]defined as patients with no liver biopsy or biopsy >2 years old that showed no cirrhosis
[b]defined as liver biopsy showing no scarring to marked fibrosis, METAVIR score of 0-3
[c]liver biopsy, definite ultrasound or CT scan demonstrating cirrhosis but no clinical signs of decompensation
[d]cirrhosis and at least one event of variceal haemorrhage, ascites, or hepatic encephalopathy
[e]carcinoma demonstrated by liver biopsy or CT scan
[f]to interferon monotherapy or interferon and ribavirin combination and HCV RNA negative 6 months post treatment

Country/ setting

What is the country and setting for the evaluation?

Canada, outpatient centres.

Data Sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review / synthesis or combination of previous studies, expert opinion?

Single observational study. In addition, a publication by Thompson Coon et al applied UK social preference weights to the individual patient data for the compensated cirrhosis, decompensated cirrhosis, and HCC data from the Chong study (see below).

Results

Summarise the results

Mean utility (95% CI)	No biopsy	Mild/moderate HCV	Compensated cirrhosis	Decompensated cirrhosis	HCC	Transplant	SVR
Chong	0.73 (0.62, 0.83)	0.76 (0.68, 0.83)	0.74 (0.66, 0.83)	0.66 (0.46, 0.86)	0.65 (0.44, 0.86)	0.69 (0.62, 0.77)	0.83 (0.77, 0.90)
Thompson Coon	-	-	0.75 (0.66, 0.83)	0.66 (0.46, 0.86)	0.64 (0.44, 0.86)	-	-
Canadian population norms: 0.821 (95% CI 0.810, 0.832). Statistically significant differences in EQ-5D and Canadian populations norms were seen in all groups except the SVR group.							

Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

Yes

Mapping

If a model was used, describe the type of model (eg. regression) or other conversion algorithm

Not applicable

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

Quality of life differences across the HCV spectrum are small, however is significantly diminished when compared to population norms.

What are the implications of the study for the model

Provide alternative utility scores.

Appendix 8 Cost-effectiveness data extraction forms for manufacturers' submissions

This record was compiled by SHTAC following the format used by the NHS CRD Economic Evaluation Database.

Study Characteristics

1 Reference (Lead author, year, refid)

MSD, 2012

1.1 Health technology

Peginterferon alfa-2b and ribavirin

1.2 Interventions and comparators

What interventions/ strategies were included?

Peginterferon alfa 2a and peginterferon alfa 2b in combination with ribavirin

Was a no treatment/ supportive care strategy included?

Best supportive care

Describe interventions/ strategies

Peginterferon alfa-2a (Pegasys) and Ribavirin (Copegus) and peginterferon alfa-2b (ViraferonPeg) and ribavirin (rebetol)

1.3 Research question

What are the stated objectives of the evaluation?

To estimate the cost effectiveness of peginterferon (Peg 2a and Peg 2b) in combination with ribavirin for the treatment of chronic HCV in children and young people aged 3 to 17 years, compared to supportive care.

1.4 Study type Cost-effectiveness/ cost-utility/ cost-benefit analysis?

Cost utility analysis

1.5 Study population

What definition was used for [condition]? What are the characteristics of the baseline cohort for the evaluation?

A baseline population of children and young people aged 5 to 17 years old with chronic HCV who were treatment-naive and had no HIV co-infection. It also included an additional analysis for 3 – 4 years olds.

1.6 Institutional setting Where is/are the intervention(s) being evaluated usually provided?

NHS secondary care

1.7 Country/ currency

Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?

UK, £ price year: 2010/2011

1.8 Funding source

MSD

1.9 Analytical perspective

What is the perspective adopted for the evaluation (health service, health and personal social services, third party payer, societal (i.e. including costs borne by individuals and lost productivity)?

NHS and Personal Social Services (PSS)

2 Effectiveness

Were the effectiveness data derived from: a single study, a review/ synthesis of previous studies or expert opinion? Give the definition of treatment effect used in the evaluation. Give the size of the treatment effect used in the evaluation

Effectiveness derived from a systematic review of the literature for the efficacy of PEG α and ribavirin, in terms of EVR and SVR. The review identified eight clinical trials in paediatric patients.[46;48;52;57;58;60;64;65] A meta-analysis was then conducted to synthesise the data by genotype.

MS (Table 25): Clinical efficacy of PEG INF and ribavirin treatment

		EVR			**SVR**		
		Proportion	**95% CI***	**Distribution and parameters**	**Proportion**	**95% CI***	**Distribution and parameters**
Genotypes 2/3	PEG α-2a	NA	NA	NA	0.84	0.69-0.95	Beta α=24.82; β=4.73
	PEG α-2b	NA	NA	NA	0.92	0.80-0.99	Beta α=27.90 β=2.43
Genotypes 1/4	PEG α-2a	0.64	0.51-0.76	Beta α=35.61; β=20.03	0.52	0.42-0.62	Beta α=49.34; β=45.55
	PEG α-2b	0.61	0.48-0.74	Beta α=32.38; β=20.70	0.51	0.45-0.58	Beta α=115.37; β=110.85

3 Intervention Costs

Were the cost data derived from: a single (observational) study, a review/ synthesis of previous studies expert opinion? Were the methods for deriving these data adequately described (give sources if using data from other published studies)? List the direct intervention costs and other direct costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

The costs consisted of treatment-related costs, including drug acquisition costs, cost associated with treatment initiation and on-treatment and post-treatment monitoring, and health states costs. Costs associated with treating adverse events were not considered in the model as they were unlikely to be substantial.

Unit prices for Peg α-2b, Peg α-2a and ribavirin were obtained from BNF 63. The dosages used were 180 µg/1.73 m^2 per week for Peg α-2a, 60 µg/m^2 per week Peg α-2b and 15 mg/kg for ribavirin The treatment cost of a course of peginterferon alfa in combination with ribavirin was

- Genotypes 2/3 (24 week treatment)
    - Age 3-4: £2,400.00 on PEG α-2b
    - Age 5-8: £3,326.20 on PEG α-2a; £3,180.42 on PEG α-2b
    - Age 9-13: £3,628.06 on PEG α-2a; £4,370.16 on PEG α-2b
    - Age 14-17: £4,558.02 on PEG α-2a; £4,554.80 on PEG α-2b
- Genotypes 1/4 (48 week treatment)
    - Age 3-4: £4,800.00 on PEG α-2b
    - Age 5-8: £6,652.40 on PEG α-2a; £6,360.84 on PEG α-2b
    - Age 9-13: £7,256.12 on PEG α-2a; £8,740.32 on PEG α-2b
    - Age 14-17: £9,116.03 on PEG α-2a; £9,109.59 on PEG α-2b

Patients incur costs associated with treatment initiation, on-treatment and post-treatment monitoring. Costs were based upon previous NICE technology assessment[33;34] with adjustment to reflect the experience of a child or young person with HCV as advised by experts. Prices were inflated from 2003/4 to 2010/11 using the HCHS index.

MS (Table 30): Summary of treatment-related costs: treatment initiation, on-treatment and post-treatment monitoring

		Cost (by age group)	**Notes**
Treatment initiation	Initial evaluation	£355.23	Applied to all patients
	Investigation for treatment	3-13: £775.72 14-17: £778.79	Applied to all treated patients (on PEG α)
On-treatment monitoring	12 week treatment	3-13: 1328.20 14-17: 1340.48	Applied to all patients with HCV of genotype 1/4 who have not achieved an EVR (on PEG α)
	24 week treatment	3-13: £1,999.90 14-17: £2,021.38	Applied to all patients with genotypes 2/3 HCV (on PEG α)
	48 week treatment	3-13: £3,329.38 14-17: £3,357.00	Applied to all patients with HCV of genotype 1/4 who completed the treatment course (on PEG α)
Post-treatment monitoring	Monitoring up to 24 weeks after treatment	3-13: £249.51 14-17: £258.72	Applied to all patients who were treated (and who have achieved an EVR if genotype 1/4) and who have not progressed to HCC
	Annual surveillance	£191.11/year	Applied to those who achieved an SVR and who have not progressed to HCC; the costs were applied from the year after treatment for five years for patients who had mild/moderate HCV and lifetime for patients who had cirrhotic HCV.

Health state costs were used from the previous NICE technology assessment of the treatment of chronic HCV in adults.[33;34] Health state costs were inflated to 2010/11 using the HCHS index.

MS (Table 32): List of health states and associated costs in the economic model

Health state	**Annual costs (in 2010-11 £)**	**95% CI**	**Distribution and parameters**
SVR from mild or moderate HCV	£132.18	£99-£165	NA

SVR from compensated cirrhosis	£191.11	£143-£239	NA
Mild HCV	£178	£109-£247	Gamma k=25.70; θ=5.37
Moderate HCV	£926	£733-£1,119	Gamma k=88.85; θ=8.07
Compensated cirrhosis	£1,469	£884-£2,054	Gamma k=24.23; θ=46.96
DC	£11,775	£7,930-£15,620	Gamma k=36.03; θ=253.13
HCC	£10,492	£5,659-£15,325	Gamma k=18.11; θ=448.80
Liver transplant	£47,495	£33,748-£61,242	Gamma k=89.75/13.78; θ=304.50/686.42
Post-liver transplant	£1,788	£890-£2,686	Gamma k=15.22; θ=91.01

indicate the source for individual cost values (if appropriate)

3.1 Indirect Costs (costs due to lost productivity, unpaid inputs to patient care)

Were indirect costs included:

None included

4 Health state valuations/ utilities (if study uses quality of life adjustments to outcomes)

Were the utility data derived from: a single (observational) study, a review/ synthesis of previous studies expert opinion. Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

A systematic literature review on the HRQoL of children and young people with HCV identified six studies, however none of these were appropriate to be used in the analysis. Adult values were identified as the most appropriate estimates. The utility weights were obtained from published NICE technology appraisals.[33;34]

4.1 List the utility values used in the evaluation

MS (Table 27): Summary of health state utilities for the cost-effectiveness analysis

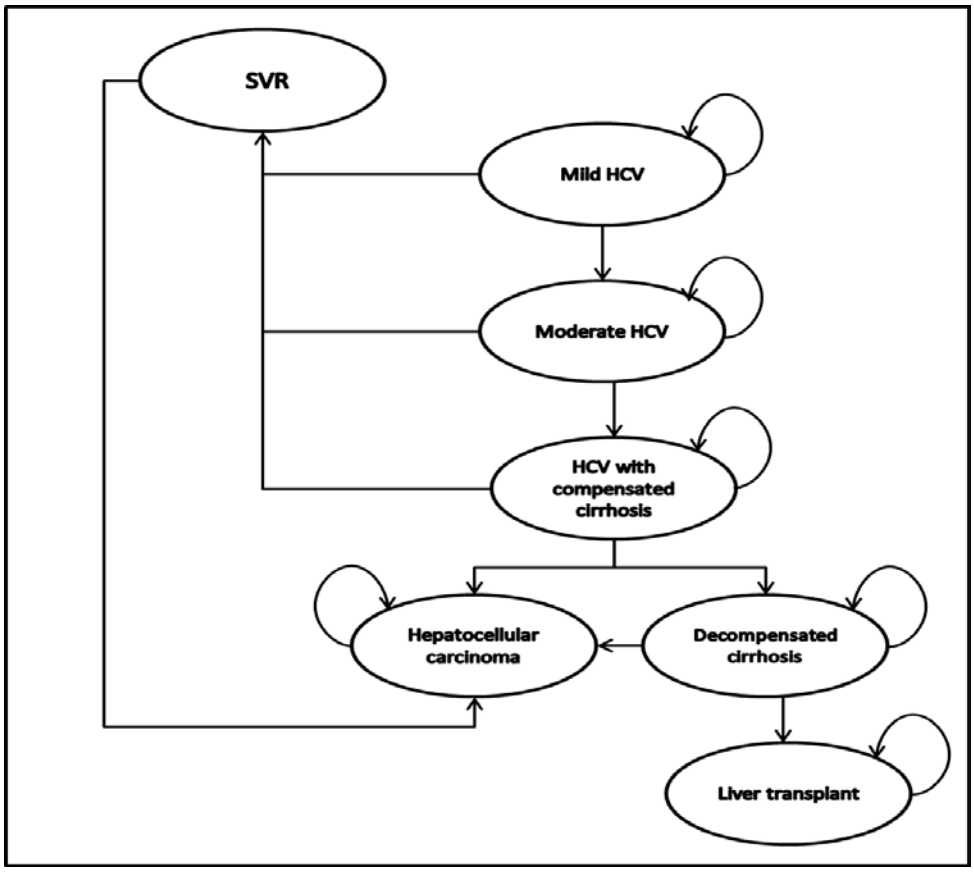
Health State	**Utility weight**	**95% CI**	**Distribution and parameters**
Mild HCV	0.77	0.74-0.80	Beta α=521.24; β=155.69
Moderate HCV	0.66	0.60-0.72	Beta α=168.25; β=86.67
Compensated cirrhosis	0.55	0.45-0.65	Beta α=47.10; β=38.54
SVR from mild HCV	0.82	0.74-0.90	Beta α=65.87; β=14.46
SVR from moderate HCV	0.72	0.62-0.82	Beta α=58.06; β=22.58
SVR from compensated cirrhosis	0.61	0.51-0.71	Beta α=58.05; β=37.11
DC	0.45	0.39-0.51	Beta α=123.75; β=151.25
HCC	0.45	0.39-0.51	Beta α=123.75; β=151.25
Liver transplant	0.45	0.39-0.51	Beta α=123.75; β=151.25
Post-liver transplant	0.67	0.57-0.77	Beta α=59.25; β=29.19
Disutility due to adverse events	0.11	NA	NA

indicate the source for individual cost values (if appropriate)

5 Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation). Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original. What was the purpose of the model (i.e. why was a model required in this evaluation)? What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.

A state-transition Markov model was developed based on the model structure used in the economic evaluation for TA200. [20;41] The model includes seven non-absorbing health states and an absorbing death state as shown in the figure:



Patients enter the model with mild HCV, moderate HCV or compensated cirrhosis and are eligible to receive treatment in cycle one. The cycle length of the model was one year except for the first year. In the first year patients receive treatment for either 12, 24 or 48 weeks depending on the futility rule and genotype. For genotype 2 and 3 patients, the first year was split into two cycles:

1. The first 24 weeks where all patients receive treatment
2. The following weeks until the end of the year where patients who do not achieve SVR stay in the same HCV state or progress to a more severe disease state. Those who achieve SVR move to the corresponding SVR state.

For genotypes 1 and 4, the first year was split into three cycles:

1. The first 12 weeks where patients are assessed for the futility rule (EVR). Patients terminate treatment if do they do not achieve EVR.

2. The following 36 weeks where patients who did achieve EVR remain on treatment. Those who did not achieve EVR remain in the same HCV state or progress to a more severe disease state.
3. The following weeks until the end of the year where patients who do not achieve SVR stay in the same HCV state or progress to a more severe disease state. Those who achieve SVR move to the corresponding SVR state.

Patients with SVR are considered to be 'cured' and at no further risk of more severe disease, except for those in the SVR with compensated cirrhosis state who have an excess risk of developing HCC.

The mortality rates from all three SVR health states, mild HCV, moderate HCV and compensated cirrhosis are assumed to be the same as for the general population. Patients with decompensated cirrhosis, HCC and those who receive a liver transplant face a higher risk of mortality than the general population.

Liver transplant is also split into two states, 'liver transplant' and 'post-liver transplant'. Patients remain in the liver transplant state for one cycle then transition to the post-liver transplant state where they either remain or transition to the death state.

In line with previous economic evaluations, the following assumptions were made:
- The model did not account for re-infection and onward transmission of HCV
- The possibility of HCC patients receiving a liver transplant was not considered due to its rarity.

A systematic review was undertaken for the natural history of HCV in children and young people. Data was extracted from the seven studies[12;76;91-95] identified and then pooled to give an estimate for the annual transition probability between mild HCV and moderate HCV and moderate HCV and compensated cirrhosis. The transition probabilities used in the model for all other transitions were the same as for the previous NICE appraisals.[33;34]

5.1 Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).

MS (Table 24): Transition probabilities utilised in the cost-effectiveness model

Health state		**Transition probability**		
From	**To**		**95% CI**	**Distribution and parameters**
SVR (CC)	SVR (CC)	#	#	#
	HCC	0.014	0.0000-0.0335	Beta α=1.93; β=136.11
Mild HCV	Mild HCV	#	#	#
	Moderate HCV	0.0257[a] / 0.025[b]	0.0187-0.0348	Beta α=38.12; β=1445.26
Moderate HCV	Moderate HCV	#	#	#
	CC	0.0038[a] / 0.037[b]	0.0018-0.0079	Beta α=5.94; β=1556.36
CC	CC	#	#	#
	DC	0.039	0.0194-0.0586	Beta α=14.62; β=360.17
	HCC	0.014	0.0000-0.0335	Beta α=1.93; β=136.11
DC	DC	#	#	#
	HCC	0.014	0.0000-0.0335	Beta α=1.93; β=136.11
	Liver transplant	0.020	0.0182-0.0418	Beta α=10.87; β=532.58
	Death*	0.130	0.1104-0.1496	Beta α=147.03; β=983.97
HCC	HCC	#	#	#

	Death*	0.430	0.3713-0.4887	Beta α=117.10; β=155.23
Liver transplant	Liver transplant	#	#	#
	Death*	Yr 1: 0.150; Yr 2+:0.057	Yr 1: 0.1218-0.2982; Yr 2+: 0.0344-0.0796	Yr 1: beta α=9.29; β=52.67 Yr 2+: beta α=22.90; β=378.88

As the complement of the other transition probabilities for each health state
* Excessive mortality, which is applied on top of the mortality in the general population.
[a] Value shown for adults [b] Value shown for children

5.2 What is the model time horizon?

Lifetime (until 100 years of age)

5.3 What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

An annual discount rate of 3.5% was applied to future costs and health outcomes.

5.3 List assumptions used in the model

- The base case analysis did not take into account spontaneous viral clearance
- The model did not account for re-infection and onward transmission of HCV
- The possibility of HCC patients receiving a liver transplant was not considered due to its rarity
- It was assumed that the treatment would discontinue if an EVR (i.e. undetectable HCV-RNA at treatment week 12) was not achieved at week 12
- Discontinuation due to adverse events was not accounted for as it is considered rare
- It was assumed that patients not achieving an SVR could experience disease progression from treatment initiation (genotypes 2/3) or from EVR (at week 12, genotypes 1/4)
- Adult transition probabilities (except for the transitions from mild to moderate and from moderate to compensated cirrhosis), utility weights and health state costs (except for SVR state costs) were applied to paediatric patients due to the lack of data
- Costs associated with the management of adverse events were not accounted as they were unlikely to be substantial

6 Results/ Analysis

What measure(s) of benefit were reported in the evaluation?

Cost per QALY gained. Results presented for the whole group and also by age group and genotype.

6.1 Provide a summary of the clinical outcome/ benefits estimated for each intervention/ strategy assessed in the evaluation

	All patients (5-17 years)	**Genotype 2/3**	**Genotype 1/4**
	Total QALYs	**Total QALYs**	**Total QALYs**
Supportive care	16.77	16.77	16.77
PEG α-2a	19.16	20.02	18.73
PEG α-2b	19.24	20.33	18.7

6.2 Provide a summary of the costs estimated for each intervention/ strategy assessed in the evaluation

	All patients (5-17 years)	Genotype 2/3	Genotype 1/4
	Total costs	**Total costs**	**Total costs**
Supportive care	£22,750	£22,750	£22,750
PEG α-2a	£17,798	£11,837	£20,778
PEG α-2b	£17,526	£10,385	£21,097

6.3 Synthesis of costs and benefits – are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.

For all patients (5-17 years)	**Vs. supportive care**			
	Incremental costs	**Incremental LYG**	**Incremental QALYs**	**ICER**
Supportive care	-	-	-	-
PEG α-2a	-£4,952	7.69	2.39	Dominates
PEG α-2b	-£5,224	7.94	2.47	Dominates

For all patients (5-17 years)	**Peg α-2b Vs. Peg α-2b**			
	Incremental costs	**Incremental LYG**	**Incremental QALYs**	**ICER**
PEG α-2a	-	-	-	-
PEG α-2b	-£271	0.24	0.08	Dominates

6.4 Give results of any statistical analysis of the results of the evaluation.

None

6.5 Was any sensitivity analysis performed – if yes, what type(s) (i.e. deterministic (one-way, two-way etc) or probabilistic).

Deterministic and probabilistic sensitivity analyses

6.6 What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

For DSA the following scenarios were tested: spontaneous viral clearance, time horizon, efficacy of PEG 2a and 2b, transition probabilities, costs associated with treatment initiation, monitoring and health state costs, health state utility weights and disutility due to treatment, discount rates.
For PSA, the efficacy of Peg 2a, Peg 2b, transition probabilities, health states costs and health state utilities were included.

6.7 Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?

The deterministic sensitivity analysis presented results for PEG α-2b vs. PEG α 2a and vs. BSC. The deterministic sensitivity analysis results showed that PEG α-2b dominated BSC in nearly all base case analyses, except for time horizon and for discount rates. The ICERs for PEG α-2b versus PEG α-2a were robust to variation in the model parameters, i.e. PEG α-2b dominated PEG α-2a for all analyses. The results of all PSA showed there is 100% certainty that PEG α-2a and PEG α-2b in combination with ribavirin are cost effective compared to BSC.

7 Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

PEG α-2a and PEG-2b in combination with ribavirin are cost effective treatment options for children and young people (5-17 years) with HCV compared to supportive care

8 SHTAC Commentary

Selection of comparators:

Appropriate

Validity of estimate of measure of benefit:

Appropriate, based upon previous HTA reports

Validity of estimate of costs:

Appropriate, based upon previous HTA reports

This record was compiled by SHTAC following the format used by the NHS CRD Economic Evaluation Database.

Study Characteristics

1 Reference (Lead author, year, refid)

Roche, 2012

1.1 Health technology

Peginterferon alfa 2a and ribavirin

1.2 Interventions and comparators

What interventions/ strategies were included?

Peginterferon alfa 2a and ribavirin

Was a no treatment/ supportive care strategy included?

Best supportive care

Describe interventions/ strategies

Peginterferon alfa-2a (Pegasys) and Ribavirin (Copegus). Doses were 180 µg/ 1.73 m^2 surface area (BSA) subcutaneously once weekly for peginterferon and 15 mg/kg orally twice daily.

1.3 Research question

What are the stated objectives of the evaluation?

To estimate the cost effectiveness of peginterferon (PEG) in combination with ribavirin for the treatment in children and young people with HCV, compared to supportive care.

1.4 Study type Cost-effectiveness/ cost-utility/ cost-benefit analysis?

Cost utility analysis

1.5 Study population

What definition was used for [condition]? What are the characteristics of the baseline cohort for the evaluation?

A baseline population of children aged 11 years old with HCV who were treatment-naive and had no HIV co-infection. The proportion of patients that enter with mild and moderate disease is based upon a weighted average from the four named clinical trials.

1.6 Institutional setting Where is/are the intervention(s) being evaluated usually provided?

NHS secondary care

1.7 Country/ currency

Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?

UK, £ price year: 2010/2011

1.8 Funding source

Roche

1.9 Analytical perspective

What is the perspective adopted for the evaluation (health service, health and personal social services, third party payer, societal (i.e. including costs borne by individuals and lost productivity)?

NHS and Personal Social Services (PSS)

2 Effectiveness

Were the effectiveness data derived from: a single study, a review/ synthesis of previous studies or expert opinion? Give the definition of treatment effect used in the evaluation. Give the size of the treatment effect used in the evaluation

Treatment efficacy was estimated for SVR as a weighted average of the four clinical trials for PEG alfa 2a.

MS (Table 10). Treatment efficacy and withdrawal

	Genotypes 1/4/5/6		**Genotypes 2/3 (48 weeks treatment)**		**Genotypes 2/3 (24 weeks treatment)**
	SVR	Drop-out	SVR	Drop-out	SVR
Schwarz et al.[57]	47%	29%	80%	10%	-
Sokal et al. [58]	57%	17%	-	-	89%
Sluzewski et al.[66]	78%	NR	-	-	75%
Abdel-Hady et al.[67]	56%	NR	-	-	90%
Weighted average	**59%**	**23%**	**80%**	**10%**	**89%**

NR not reported

Spontaneous SVR was included for the no treatment group based upon a rapid review of the literature by the manufacturer. The risk of spontaneous SVR differs between how the infection was acquired: through vertical transmission (VT) at birth or other means (non-VT) during infancy or childhood. The annual probability of spontaneous SVR was 1.65% for non-VT and 2.37% for VT according to evidence from the European Paediatric Hepatitis C Virus Network (EPHCVN). Spontaneous SVR among non-VT occurs during the first five years of infection.

3 Intervention Costs

Were the cost data derived from: a single (observational) study, a review/ synthesis of previous studies expert opinion? Were the methods for deriving these data adequately described (give sources if using data from other published studies)? List the direct intervention costs and other direct costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

The costs consisted of treatment-related costs, including drug acquisition costs, cost associated with treatment initiation and on-treatment and post-treatment monitoring, and health states costs.

Unit prices for the treatments were obtained from BNF 63. The doses used in the analysis were in line with the dosing schedule in the relevant clinical trials. Body surface area was estimated using the Dubois formula. The MS estimated doses for different patient ages and hence cost for these cohorts

(MS Table 16).

Drug costs for PEG-IFN α-2a were calculated for a dosage of 180 μg/ 1.73 m^2 body surface area (BSA) (max 180 μg) subcutaneously once weekly. Ribavirin (as Copegus) was administered in a dose of 15 mg/kg orally twice daily (max 1200 mg/day if ≥75 kg and 1000 mg if <75 kg).

No syringe sharing was assumed in the model, therefore, wastage was included in the calculation of cost. For all treatments the most efficient vial/syringe to deliver the dose was assumed (i.e. that which produced the least wastage). In other words, if the dose for PEG-IFN α-2a was estimated to be 125 μg, then one 135 μg pre-filled syringe was used. Similarly, if the dose was estimated to be 137 μg, then the next larger syringe (180 μg) was used.

In the base case the estimated costs for 48 weeks of combination therapy are £8,307.

MS (Table 16). Mean doses and weekly costs for treatments

Cohort age (years)	**Weekly dose PEG-IFN α-2a (μg)**	**Daily dose Ribavirin (mg)**	**Weekly cost PEG-IFN α-2a+RBV**
5	83.27	311.13	£95.82
6	91.42	352.30	£134.92
7	100.69	404.00	£138.90
8	107.53	440.19	£141.69
9	117.29	498.96	£146.22
10	125.71	550.11	£150.16
11*	137.42	631.27	£173.06
12	150.58	728.37	£180.54
13	159.56	787.98	£185.14
14	171.29	880.58	£192.28
15	176.45	925.58	£195.75
16 to 24	180	1000	£201.48

*The MS base case cohort starting age is 11 years

The economic model incorporates a costing protocol developed as part of a previously developed health technology assessment report to estimate the appropriate evaluation, monitoring and surveillance cost. They inflated costs to 2010–11 values using the HCHS Pay and Prices Index.[74]

In total, treatment monitoring costs were £564 for 24 weeks of treatment and £811 for 48 weeks of treatment.

Health state costs were used from the previous NICE technology assessments of the treatment of HCV in adults.[20;41] Health state costs were inflated to 2010/11 using the HCHS index.[74]

List of health states and associated costs in the economic model

Health state	**Annual costs (in 2010-11 £)**
SVR	0
Mild HCV	£178
Moderate HCV	£926
Compensated cirrhosis	£1,470
DC	£11,780
HCC	£10,496
Liver transplant	£47,513
Post-liver transplant	£1,789

indicate the source for individual cost values (if appropriate)

3.1 Indirect Costs (costs due to lost productivity, unpaid inputs to patient care)

Were indirect costs included:

None included

4 Health state valuations/ utilities (if study uses quality of life adjustments to outcomes)

Were the utility data derived from: a single (observational) study, a review/ synthesis of previous studies expert opinion. Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

A systematic literature review on the HRQoL of children and young people with HCV identified two partially applicable studies reporting utilites of children with chronic HCV, but both were based an expert's Time Trade Off (TTO) values for adults with chronic HCV. Adult values were identified as the most appropriate estimates. The utility weights were obtained from published NICE technology appraisals.[20;41]

Health state utilities were estimated in a stepwise fashion:

1. Baseline utilities for the general population were estimated.
2. A utility multiplier was derived by comparing the health state utility from the literature to the utility of the general population with the same age and gender composition.
3. Utility multipliers (from step 2) were applied to baseline utilities (from step 1) corresponding to the model cohort age and gender composition

For children under the age of 17 years old the economic model applied a baseline utility of 0.95 based on a study by Saigal and colleagues. For the healthy population who are 17 years old and above, they applied the utilities of adults derived using a model developed by Ara and Brazier.

4.1 List the utility values used in the evaluation

MS Table 19. EQ-5D derived utility weights from previous health technology assessments for adults

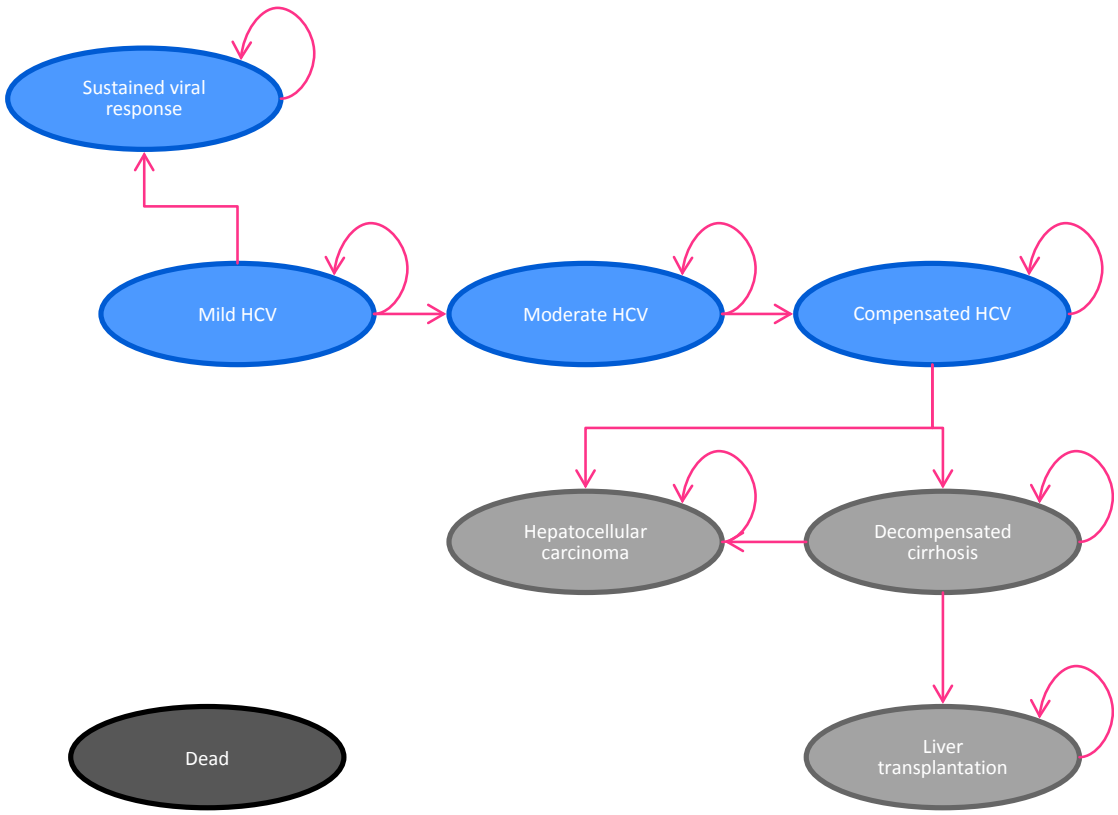
	Mean utility	**Mean age**	**% of male**	**Source**
Healthy children (≤ 16 years old)	0.95	-	-	Saigal et al. [77]
SVR after mild disease	0.83	39.8	52%	Wright et al. [83]
Treatment for mild disease	0.66			
Mild disease	0.77			
Treatment for moderate disease	0.55			
Moderate disease	0.66			
Cirrhosis	0.55			
Decompensated cirrhosis and HCC	0.45			
Post-liver transplantation	0.67			

5 Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation). Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original. What was the purpose of the model (i.e. why was a model required in this evaluation)? What are the main components of the model (e.g. health

states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.

A state-transition Markov model was developed based on the model structure used in the economic evaluation for TA200[34;40] The model includes seven non-absorbing health states and an absorbing death state as shown in the figure:



In the model, sustained viral response (SVR) is assumed to be a permanent condition (i.e. cure) with no spontaneous reactivation of HCV infection. The diagram indicates that in the absence of successful treatment or spontaneous clearance, patients with HCV may remain in their current health state or move on to increasingly severe stages of liver disease (decompensated cirrhosis, hepatocellular carcinoma (HCC) and liver transplantation). Transitions to death can happen from any health state. Individuals in the blue health states (SVR, mild and moderate fibrosis and compensated cirrhosis) are assumed to face the same mortality risks as the general population; individuals in the grey health states (decompensated cirrhosis, HCC and liver transplantation) face excess mortality risks attributable to chronic liver disease.

5.1 Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).

Probabilities of disease progression applied in the model

Parameters	**Annual probability**	**Source**
Spontaneous SVR – VT	0.237	European Paediatric Hepatitis C Virus Network 2005
Spontaneous SVR – non-VT	0.016	Literature review

Mild–moderate disease	0.014	Guido et al.[76]
Moderate disease–cirrhosis	0.021	Estimation based on Guido et al.[76] and Wright et al.[83]
Cirrhosis–decompensated cirrhosis	0.040	Wright et al. [83]
Cirrhosis or decompensated cirrhosis–HCC	0.014	Wright et al. [83]
Decompensated cirrhosis–death	0.130	Wright et al. [83]
HCC–death	0.430	Wright et al. [83]
Decompensated cirrhosis–liver transplant	0.020	Wright et al. [83]
Liver transplant–death (year 1)	0.160	Barshes et al.[96]
Liver transplant–death (subsequent years)	0.038	Barshes et al.[96]
All-cause death	Time-dependent	ONS 2011: UK life table

5.2 What is the model time horizon?

30 years, which was considered long enough to capture important costs and effects arising from treatment.

5.3 What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

An annual discount rate of 3.5% was applied to future costs and benefits.

5.3 List assumptions used in the model

- Efficacy and discontinuation data for patients with moderate HCV at baseline was not available from the literature; therefore it was assumed that stage of fibrosis would not impact the probability of SVR.
- It was assumed that these AEs may impact health-related quality of life, but were unlikely to require additional resource use.
- Based on interviews with clinical experts during the development of the economic model, no HCV related costs were assumed to accrue to patients achieving SVR.

6 Results/ Analysis

What measure(s) of benefit were reported in the evaluation?

Cost per QALY gained. Results presented by genotype.

6.1 Provide a summary of the clinical outcome/ benefits estimated for each intervention/ strategy assessed in the evaluation

Treating genotypes 1, 4 and 5 patients with PEG IFN alfa-2a and ribavirin improved outcomes by 1.01 QALYs compared to BSC. For genotypes 2 and 3, treatment for 24 weeks improved QALYs by 1.57 compared to BSC.

6.2 Provide a summary of the costs estimated for each intervention/ strategy assessed in the evaluation

Treating genotypes 1, 4 and 5 patients with PEG IFN alfa-2a and ribavirin cost an additional £3,971 compared to BSC. For genotypes 2 and 3, treatment for 24 weeks cost £1,834 less compared to BSC.

6.3 Synthesis of costs and benefits – are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.

MS Table 22. Base case cost-effectiveness of PEG-IFN α-2a+RBV combination therapy in patients with chronic HCV

Treatment	Cost (£)	Outcome (Life Years)	Outcome (QALYs)	ICER (£/QALY gained)
Genotype 1, 4 and 5				
No Treatment	£8,199	18.47	14.20	
PEG-IFN α-2a+RBV	£12,170	18.56	15.21	
Inc emental	£3,971	0.09	1.01	£3,915
Genotype 2 and 3				
No Treatment	£8,199	18.47	14.20	
PEG-IFN α-2a+RBV 24 wk.	£6,336	18.61	15.77	
PEG-IFN α-2a+RBV 48 wk.	£11,010	18.60	15.61	
Incrementals				
PEG-IFN α-2a+RBV 24 wk. vs. no treatment	-£1,864	0.14	1. 7	Dominates no treatment
PEG-IFN α-2a+RBV 24 wk. vs. 48 wk.	£4,675	-0.01	-0.16	Dominated by 24 wk.

6.4 Give results of any statistical analysis of the results of the evaluation.

None

6.5 Was any sensitivity analysis performed – if yes, what type(s) (i.e. deterministic (one-way, two-way etc) or probabilistic).

Deterministic and probabilistic sensitivity analyses

6.6 What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states), methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

The following sensitivity analyses were performed: likelihood of spontaneous viral clearance, time horizon, discounting, age at entry to the model, distribution of fibrosis at entry to model, rate of disease progression from mild to moderate fibrosis to compensated cirrhosis, probability of SVR with treatment, health state costs, health state utilities, timing of treatment.

6.7 Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?

The cost effectiveness of PEG alfa 2a remains below £10,000 per QALY for all analyses, except for the use of a time horizon of 15 years (ICER of £12,010 per QALY for genotypes 1, 4, and 5). Model

results are most sensitive to time horizon, the rate of disease progression, probability of SVR with treatment, the distribution of SVR with treatment, distribution of patients across liver disease stages at entry to the model and annual cost of achieving SVR. In the PSA, for patients with genotypes 2 and 3, there is a 97.2% probability of 24 weeks of combination therapy being cost effective compared to no treatment at a willingness to pay threshold of £20,000 per QALY. In patients with genotype 1, 4 and 5 there is a probability of 91.6% of being cost effective at a £20,000/QALY threshold.

7 Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

PEG alfa-2a in combination with ribavirin is cost effective treatment options for children and young people with HCV compared to best supportive care

8 SHTAC Commentary

Selection of comparators:

Appropriate

Validity of estimate of measure of benefit:

Appropriate, based upon previous HTA reports

Validity of estimate of costs:

Appropriate, based upon previous HTA reports

Appendix 9 Critical appraisal checklist of economic evaluation

The Roche and MSD MS were appraised for methodological quality and generalisability to the UK NHS using a checklist adapted from the NICE reference case requirements,[70]and the Philips and colleagues' checklist.[45]

	Item	MSD	Roche
1	Is there a clear statement of the decision problem?	Yes	Yes
2	Is the comparator routinely used in UK NHS?	Yes	Yes
3	Is the patient group in the study similar to those of interest in UK NHS?	Yes	Yes
4	Is the health care system comparable to UK?	Yes	Yes
5	Is the setting comparable to the UK?	Yes	Yes
6	Is the perspective of the model clearly stated?	Yes	Yes
7	Is the study type appropriate?	Yes	Yes
8	Is the modelling methodology appropriate?	Yes	Yes
9	Is the model structure described and does it reflect the disease process?	Yes	Yes
10	Are assumptions about model structure listed and justified?	Yes	Yes
11	Are the data inputs for the model described and justified?	Yes	Yes
12	Is the effectiveness of the intervention established based on a systematic review?	Yes	Yes
13	Are health benefits measured in QALYs?	Yes	Yes
14	Are health benefits measured using a standardised and validated generic instrument?	Yes	Yes
15	Are the resource costs described and justified?	Yes	Yes
16	Have the costs and outcomes been discounted?	Yes	Yes
17	Has uncertainty been assessed?	Yes	Yes
18	Has the model been validated?	No	No

Yes / No / ? (unclear)

Appendix 10 Probabilistic sensitivity analysis variables

Variables and Probability distributions used in the probabilistic sensitivity analyses

Name	*Mean value*	*standard error*	*distribution*	*alpha*	*beta*
Patient distribution					
Patients with Genotype 1 + 4 (Peg 2a)	0.77	0.05	*Beta*	53.8	16.1
Patients with Genotype 2 + 3 (Peg 2a)	0.23	0.07	*Beta*	8.1	27.1
Patients with Genotype 1 + 4 (Peg 2b)	0.82	0.04	*Beta*	74.8	16.4
Patients with Genotype 2 + 3 (Peg 2b)	0.18	0.05	*Beta*	10.4	47.6
Treatment effect					
EVR for genotype 1 and 4 (Peg 2a)	0.57	0.05	*Beta*	49.2	37.1
EVR for genotype 1 and 4 (Peg 2b)	0.61	0.04	*Beta*	91.0	58.2
SVR at Age 11	0.00				
SVR for genotype 1 and 4 (Peg 2a)	0.52	0.06	*Beta*	39.43	36.40
SVR for genotype 2 and 3 (Peg 2a)	0.86	0.07	*Beta*	22.91	3.73
SVR overall (all genotypes) (Peg 2a)	0.60	0.06	*Beta*	42.21	28.14
SVR for genotype 1 and 4 (Peg 2b)	0.51	0.04	*Beta*	79.15	76.04
SVR for genotype 2 and 3 (Peg 2b)	0.91	0.05	*Beta*	32.83	3.25
SVR overall (all genotypes) (Peg 2b)	0.58	0.03	*Beta*	121.64	88.09
Transition probabilities					
F0 state to F1	0.12	0.01	*Beta*	274.62	2072.54
F1 state to F2	0.09	0.01	*Beta*	230.28	2478.89
F2 state to F3	0.12	0.01	*Beta*	337.99	2478.60
F3 state to F4	0.12	0.01	*Beta*	292.30	2227.52
F4 state to decompensated cirrhosis	0.04	0.01	*Beta*	14.58	359.21
F4 state to HCC	0.01	0.01	*Beta*	1.92	135.12
DC to HCC	0.01	0.01	*Beta*	1.92	135.12
DC to liver transplant	0.02	0.01	*Beta*	15.66	767.34
DC to death related to Hepatitis C	0.13	0.01	*Beta*	146.90	983.10
HCC to death	0.43	0.03	*Beta*	116.67	154.66
Liver transplant to death	0.15	0.02	*Beta*	84.85	480.82
Post-transplant state to death	0.06	0.01	*Beta*	122.50	2026.54
Health state utility value					
Utility of SVR from mild disease	0.82				
Utility of F0 / F1	0.82				
Utility of F2 / F3	0.82				
Utility of patients in F0 / F1 receiving treatment	0.71	0.02	*Beta*	435.91	178.05

Utility of patients in F2 / F3 receiving treatment	0.71	0.02	*Beta*	435.91	178.05
Utility of patients in F4	0.75	0.02	*Beta*	237.05	79.02
Utility of patients in F4 receiving treatment	0.64	0.04	*Beta*	109.81	61.77
Utility of patients with decompensated cirrhosis	0.66	0.04	*Beta*	110.28	56.81
Utility of patients with hepatocellular cancer	0.64	0.10	*Beta*	14.74	8.29
Utility of patients in post- liver transplant state	0.69	0.03	*Beta*	163.30	73.37
Utility of patients receiving liver transplant	0.73	0.05	*Beta*	56.82	21.02
Monitoring costs					
For patients receiving 12 weeks of treatment	£721	£71	*Gamma*	£102.77	7.02
For patients receiving 16 weeks of treatment	£869	£86	*Gamma*	£102.79	8.45
For patients receiving 24 weeks of treatment	£880	£87	*Gamma*	£102.70	8.57
For patients receiving 48 weeks of treatment	£1,168	£115	*Gamma*	£102.79	11.36
For patients receiving 72 weeks of treatment	£1,155	£114	*Gamma*	£102.87	11.23
Health state cost					
Health state cost for SVR	£346	£48	*Gamma*	51.42	6.73
Health state cost for F0 / F1	£184	£27	*Gamma*	45.69	4.03
Health state cost for F2 F3	£959	£76	*Gamma*	158.93	6.03
Health state cost for F4	£1,521	£231	*Gamma*	43.29	35.13
Health state cost for DC	£12,193	£1,519	*Gamma*	64.39	189.35
Health state cost for HCC	£10,865	£1,910	*Gamma*	32.36	335.71
Health state cost for LT1 (year of liver transplant)	£32,732	£3,296	*Gamma*	98.61	331.92
Health state cost for LT2 (post-transplant)	£1,852	£355	*Gamma*	27.21	68.06

Appendix 11 Net benefit approach

Cost-effectiveness decision rules and the incremental cost effectiveness ratio

In traditional cost effectiveness analyses standard decision rules are considered to establish the cost-effectiveness of an intervention compared with a given comparator. These are typically outlined using the cost-effectiveness plane. If the incremental cost is negative and the incremental effect is positive (SE Quadrant), the intervention is unequivocally cost-effective (it is dominant, achieving better outcomes at lower cost). If the incremental cost is positive and the incremental effect is negative (NW Quadrant), the intervention is unequivocally not cost-effective (it is dominated, achieving poorer outcomes at higher cost). Where **both** the incremental cost and the incremental effect are negative (SW Quadrant), or **both** the incremental cost and the incremental effect are positive (NE Quadrant) no such unequivocal statements can be made. Determining whether the intervention is cost-effective depends on a threshold value, defined as the maximum amount society is willing to pay for an incremental health gain or equivalently as the minimum amount society is willing to accept for foregoing an incremental health gain.

One of the drawbacks of the ICER is that the location of negative ICERs (whether they are in the SE [dominant] or NW [dominated] quadrant) cannot be determined without reference to other contextual information. The incremental net benefit (INB) provides an unambiguous decision rule, although this implies knowledge of the threshold value.

For further explanation see Appendix 8 of the previous health technology assessment report.