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Pegylated interferon alpha 2a and 2b in combination with ribavirin in the treatment of chronic hepatitis C : a systematic review

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Please note:

One of the sponsors submitted information to the National Institute for Clinical Excellence in confidence and references to this information and other academic in confidence data have been removed from the report. However, it should be noted that the Institute's Appraisal Committee had access to the full report when drawing up their guidance.

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A note about terminology

Different terms have been used for pegylated interferon, interferon and ribavirin in the text of this report. This has been done in an attempt to maximise clarity for the reader. In the narrative sections of the report (e.g. section 2 - Background) the drugs have generally been referred to by their full names (e.g. pegylated interferon). In the methods and results sections, data extraction tables, and cost-effectiveness sections, where these terms are used very frequently, abbreviations are used (e.g. PEG, IFN, RBV). The use of abbreviations in these sections saves space and potentially avoids ambiguity in the use of the word 'interferon', which could refer to either the pegylated or non-pegylated form (N.B. we have refrained from using the term 'standard' interferon to denote the previous version of this drug. Instead the term 'non-pegylated' interferon is used).

PEG = pegylated interferon
IFN = non-pegylated interferon (what some people refer to as 'standard' interferon)
RBV = ribavirin

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Summary

Aim

The aim of this systematic review is to assess the clinical-effectiveness and cost-effectiveness of pegylated interferon alpha combined with ribavirin in the treatment of chronic hepatitis C. The comparator is the current standard of treatment, non-pegylated interferon alpha combined with ribavirin. Because some patients cannot tolerate ribavirin, treatment with pegylated interferon alpha alone is also compared with treatment with non-pegylated interferon alpha alone. Additional secondary questions are also addressed, including:

- the effectiveness of re-treating non-responders to interferon alpha monotherapy;
- use of non-invasive tests for detecting fibrosis;
- the effectiveness of anti-viral treatment of patients with mild disease.

Epidemiology and background

Hepatitis C is a slowly progressive disease of the liver that is caused by infection with the hepatitis C virus. The virus can be transmitted a number of ways, but the most common sources of infection are through injected drug use and infected blood products. Although some people infected with hepatitis C spontaneously clear the virus, up to 85% of those exposed develop chronic hepatitis. The rate of progression is slow and variable over 20-50 years. About 20-30% of those initially infected develop cirrhosis within 20 years and a small percentage of these are at high risk of hepatocellular carcinoma. Patients with chronic hepatitis C report diminished health-related quality of life, which can be improved by eradication of the virus. The prevalence of chronic hepatitis C in the UK is uncertain, but is estimated to be between 0.1% and 1%. Prevalence varies across different groups according to risk factors such as injecting drug use. Accurate prevalence rates are difficult to estimate because infection can remain asymptomatic for very long periods. There are a number of genotypes of the virus, the most common in England and Wales being 1a, 1b and 3a. Genotype 1 is harder to treat than genotypes 2 and 3.

Number and quality of studies, and direction of evidence

Thorough searches of the literature included searches of several databases including Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, Medline, and Embase. These searches revealed six studies that met the inclusion criteria of being randomised controlled trials (RCTs) involving comparisons between pegylated interferon alpha plus ribavirin and non-pegylated interferon plus ribavirin (2 trials) or pegylated interferon alone and non-pegylated interferon alone (4 trials). The primary outcome in all trials was sustained virological response (SVR) at follow-up. The trials were

generally of good quality although reporting of methodological details could have been more thorough in places.

Summary of benefits

Dual Therapy:

- In the two trials that tested pegylated interferon plus ribavirin against non-pegylated interferon plus ribavirin the combined percentage of sustained virological response was 55% (95% CI, 52%-58%) when using pegylated interferon and 46% (95% CI, 43%-49%) for non-pegylated interferon.
- When the two trials were meta-analysed the relative risk for remaining infected was reduced by 17% for pegylated interferon plus ribavirin compared with non-pegylated interferon plus ribavirin (RR: 0.83 [95% CI 0.76-0.91]).
- Response to therapy varied according to viral genotype. Patients with genotype 1 had the lowest levels of sustained virological response (42% and 46% for pegylated interferon plus ribavirin in the two trials) and patients with genotypes 2 or 3 had the highest levels of sustained virological response (82% and 76% for pegylated interferon plus ribavirin in the two trials).
- There were also variations in sustained virological response according to other prognostic variables such as baseline viral load.

Monotherapy:

- In the four trials that evaluated pegylated interferon monotherapy against non-pegylated interferon the combined sustained virological response rates were 31% (95% CI 27%-34%) for pegylated interferon and 14% (95% CI 12%-17%) for non-pegylated interferon.
- The relative risk for remaining infected with hepatitis C was reduced by 20% by the use of pegylated interferon (RR: 0.80 [95% CI, 0.76-0.85]).
- As reported in three of the trials, response to therapy varied according to viral genotype. Patients with genotype 1 had the lowest levels of sustained virological response (12% and 14% and 31% for treatment with pegylated interferon in the three trials reporting response by genotype). Only one trial differentiated patients with non-1 genotypes and reported higher response rates in patients with genotypes 4, 5, or 6 (60%) than in patients with genotype 2 or 3 (49%) when treated with pegylated interferon.
- In the two trials that considered prognostic variables, there were also variations in sustained virological response according to other prognostic variables such as baseline viral load.

Regimens involving pegylated interferon appear to be fairly well tolerated. A wide range of adverse events have been reported, but do

not differ substantially from levels of adverse events in regimens involving non-pegylated interferon.

A cost-effectiveness spreadsheet model originally developed by the Scottish Health Purchasing Information Centre (SHPIC) and used in the previous NICE assessment report of treatment for hepatitis C was updated for the calculation of costs and benefits. The model follows a hypothetical cohort of 1000 individuals with chronic hepatitis C over a 30 year period. Options that were considered included: no treatment (except symptomatically), interferon alpha plus ribavirin for 48 weeks, pegylated interferon alpha plus ribavirin for 48 weeks, interferon monotherapy for 48 weeks, pegylated interferon alpha monotherapy for 48 weeks. SVRs from the key trials were pooled and entered into the model. The results are presented in terms of costs per Quality Adjusted Life Years (QALYs) gained.

Dual therapy

- The incremental discounted cost/QALY for comparing no active treatment to 48 weeks of dual therapy with pegylated interferon and ribavirin (PEG + RBV) is £6,045. When moving from 48 weeks of dual therapy with non-pegylated interferon and ribavirin (IFN + RBV) to 48 weeks of dual therapy with PEG + RBV the figure is £12,123.
- Sub-group analyses for dual PEG + RBV therapy demonstrated that the most favourable incremental discounted cost/QALY estimates were for patients infected with genotypes 2 and 3, and with low baseline viral load (£3,921) when moving from no active treatment to dual therapy).
- Patients infected with genotype 1 and high baseline viral load had much higher estimates (£8,305, moving from no active treatment to dual therapy; £13,701, moving from dual therapy with IFN to dual therapy with PEG).
- Results of one way sensitivity analyses showed that the estimates varied according to differences in SVRs, drug costs and discount rates. For example, when SVRs were increased or decreased in line with the highest and lowest limits of the confidence interval around the pooled SVR estimate, the highest discounted incremental cost/QALY was £37,611, (lowest PEG SVR and highest IFN SVR), compared to £7,060 (highest PEG SVR and lowest IFN SVR).
- In general estimates remained under £30,000 per QALY.

Monotherapy

- The incremental discounted cost/QALY when moving from no active treatment to 48 weeks of monotherapy with pegylated interferon was £6,484. When moving from 48 weeks of monotherapy with IFN to 48 weeks of monotherapy with PEG the figure was £8,404.

- As with dual therapy, the lowest incremental cost/QALY was for patients with genotypes 2 and 3 and low baseline viral load in the range £2,641 to £4,194. The highest estimates were for patients with genotype 1 and high baseline viral load, in the range £30,701 to £29,963.

A published meta-analysis of the two pivotal pegylated dual therapy RCTs found that excluding the 19% of patients who do not achieve EVR at 12 weeks, only misses 0.6% of potential responders, and can lead to savings of 16% of the total cost of treating all patients with a full course. On the basis of these data it was recommended that only genotype 1 patients be assessed at week 12, with those not having an early viral response ceasing treatment, and those classed as having an early response completing the full 48 weeks treatment, unless remaining HCV RNA positive at week 24 in which case they should stop treatment.

A number of secondary questions were addressed:

- Because treatment of hepatitis C is far from universally successful in eradicating the hepatitis C virus, a large number of patients who have been previously treated remain infected. Completed trials using pegylated interferon have not been reported in these patients, but the efficacy of re-treatment with non-pegylated interferon plus ribavirin has been compared with interferon alone. Meta-analysis of 20 trials found that SVR in re-treatment was greater in patients given dual therapy than for those given monotherapy with interferon alone. The risk of remaining infected was reduced by 11% (RR: 0.89, 95% CI, 0.84 – 0.95) after 6 months of treatment (16 trials). The risk of remaining infected was reduced by 20% in two trials in which treatment was longer than 24 weeks (RR: 0.80, 95% CI, 0.66 – 0.96).
- Because of the possibility that treating patients with acute hepatitis C infection might prevent chronic infection, treatment of patients with acute infection was briefly considered. Again, complete trials using pegylated interferon were not available. Trials in acute groups were of poorer methodological quality, but were suggestive that eradication rates much higher than spontaneous eradication are achievable with treatment.
- Since many patients with hepatitis C have other co-morbidities such as co-infection with HIV or haemophilia, it was of interest to consider the efficacy of treatments within these patient groups. No full reports of trials using pegylated interferon were found. The existing evidence suggests that treatment efficacy in sub-populations with co-morbidities is generally similar to that in patient groups without significant co-morbidities.
- Non-invasive tests have been proposed as an alternative to biopsy. The best indicators appear to be combinations or "panels" of tests, preferably those which are routinely available in clinics. They may be most useful at the ends of the spectrum – i.e. for identifying those with serious liver damage who would be treated, and those with mild

disease who currently would not. For patients around the current treat/don't treat margin, the consensus is that liver biopsy is still often necessary, though the balance of risks is different in those with haemophilia.

- Evidence on the effectiveness of treating patients with mild disease is awaited. If it can be demonstrated that treatment significantly improves quality of life for these patients then this could be an argument for treating all those with mild disease, without necessarily the need for liver biopsy. A reduction in quality of life has been reported in chronic infection, and if treatment with combined therapy restores quality of life to normal, it may be cost-effective on those grounds alone. In addition, many pts with mild disease progress to more serious liver disease over a few years (academic in confidence data)

Conclusions

Well designed RCTs show that patients treated with pegylated interferon, both as dual therapy and monotherapy, experience higher sustained viral response rates than those treated with non-pegylated interferon. Patients with genotypes 2 and 3 experience the highest response, with rates in excess of 80%. Patients with the harder to treat genotype 1 nevertheless benefit, with up to 46% of patients experiencing a SVR in one of the trials. Pegylated interferon also appears to be cost-effective in most groups.

List of abbreviations and definitions of terms

µg	Microgram
AASLD	American Association for the Study of Liver Diseases
AFP	Alpha-fetoprotein -- a protein substance normally produced by the liver. Measurement of AFP in the bloodstream can be used as an early detection test for hepatocellular carcinoma.
AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine aminotransferase. An enzyme that indicates liver inflammation.
AMA	Amantadine hydrochloride (Lysovir, Alliance)
Ascites	Large accumulation of fluid in the cavity which surrounds the bowel
Biochemical Response	Normalisation of ALT levels often defined as < 40 UI/L
BNF	British National Formulary
CCT	Controlled clinical trial (without random allocation to study groups)
CDSC	Communicable Disease Surveillance Centre
Chem path	Chemical pathology
CI	Confidence interval
CIFN	Consensus interferon
cirrhosis	A condition in which the liver responds to injury or death of some of its cells by producing interlacing stands of fibrous tissue between which are nodules or regenerating cells.
cl	Centilitre
Compensated liver disease	Compensation is the act of making up for a functional or structural deficiency. For example, compensation for the loss of a diseased kidney is brought about by an increase in size of the remaining kidney, so restoring the urine producing capacity.
CRD	NHS Centre for Reviews and Dissemination
Decompensated liver disease	Ascites, variceal haemorrhage and hepatic encephalopathy are complications that can follow decompensated
dL	Decilitre
DNA	Deoxyribonucleic acid
DoH	Department of Health
EASL	European Association for the Study of the Liver
EOTR	End of treatment response
EuroQol	Also known as the EQ-5D instrument, used to estimate a patient's quality of life
EVR	Early Virological Response. Fall in HCV RNA by at least 2 log 10 units or to an undetectable level at week 12 of treatment (see Davis 2002)
FBC	Full blood count
fibrosis	Thickening and scarring of connective tissue, most often a consequence of inflammation or injury
FSS	Fatigue Severity Scale
GUM	Genito-Urinary Medicine
HAI	Histological Activity Index
HALT-C	Hepatitis C Anti-Viral Long Term Treatment Against Cirrhosis. A trial sponsored by the US National Institute of Diabetes and Digestive and Kidney Diseases on the long-term use of PEG in patients who failed to response to prior interferon treatment.
HAART	Highly Active Anti-Retroviral Therapy
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus

HCV-RNA	Hepatitis C virus ribonucleic acid. Genetic material that indicates the replication of the virus and therefore persistence of infection.
Hep C	Hepatitis C
Histological Response	Defined as a decrease of at least 2 points in the total score on the Histological Activity Index, where a score of 0 indicates no inflammatory changes and no fibrosis and a score of 22 indicates multilobular necrosis, marked intralobular degeneration and focal necrosis, marked portal inflammation, and cirrhosis.
HIV	Human Immunodeficiency Virus recognised as the agent that induces AIDS
HRQOL	Health-related quality of life
HTA	Health technology assessment
Hx	History
IFN	Non-pegylated interferon (either α-2a or α-2b)
IFN + RBV	Non-pegylated interferon and ribavirin given in combination during the same time period
INR	
interferon	There are several forms of interferon. Unless otherwise stated it is used in this report to refer to interferon alpha.
IDU	Injecting drug user
kg	Kilogram
LFT	Liver function tests
METAVIR	A scoring system for hepatic inflammation and fibrosis (from 0 to 4)
mg	Milligram
mins	minutes
ml or mL	Millilitre
mm^3	Cubic millimetre
MIU	Million international units
n	Number of participants
NICE	National Institute for Clinical Excellence
NIH	National Institutes of Health
NNT	Number needed to treat
non-response	Patients who do not show evidence of clearing the hepatitis C virus either during treatment or after the cessation of treatment.
NS	Not statistically significant
OP	
OR	Odds ratio
PCR	Polymerase chain reaction. A sensitive technique of molecular genetics in which the DNA of a single cell treatment polymerase enzymes is induced to replicate many times. This enables the DNA to be amplified in sufficient quantities to enable generic analysis. A negative PCR indicates absence of virus in the blood and is one indication of treatment response.
PEG	Pegylated interferon (either α-2a or α-2b)
PHLS	Public Health Laboratory Service
QALY	Quality adjusted life year
RBV	Ribavirin
RCT	Randomised controlled trial
relapse	Patients who have shown evidence of having cleared the hepatitis C virus during treatment, but who did not maintain a sustained virological response, i.e., the virus became detectable again within the follow-up period.
SF-36	Short Form 36 instrument
SR	Sustained complete response. Both a biochemical and virological response to treatment, sustained after treatment generally measured 24 weeks after treatment ends
SHTAC	Southampton Health Technology Assessment Centre

STD	Non-pegylated interferon (shorthand used in this review when applying inclusion criteria)
SVR	Sustained virological response often defined as HCV RNA <100 copies per millilitre that is maintained after treatment cessation usually measured 24 weeks after treatment stops
TAR	Technology Assessment Report
TFT	Thyroid function tests
TMA	Transcription Mediated Amplification. TMA can detect residual levels of virus less than 50 HCV RNA copies
tx	Treatment
U&E	Urea and electrolytes
Viral load	the amount of HCV RNA present in the body
Viraemia	the presence in the blood of virus
Virological response	absence of HCV-RNA on PCR
wk	week
x	times (e.g., 3x = 3 times)

1. Aim of the review

Pegylated interferon has recently been introduced for treatment of hepatitis C and has the advantage of a longer-lasting effect with once weekly dosing compared to three times a week for 'standard' non-pegylated interferon. Higher rates of sustained viral response with pegylated interferon have been observed both as monotherapy and in combination with ribavirin, although it is also more expensive.

The aim of this technology assessment report (TAR) is therefore to assess the clinical-effectiveness and cost-effectiveness of pegylated interferon alpha in combination with ribavirin in the treatment of chronic hepatitis C. The comparator is the current standard treatment, dual therapy with non-pegylated interferon alpha and ribavirin. For patients who cannot tolerate ribavirin the comparison is between monotherapy with pegylated and non-pegylated interferon alpha.

2. Background

2.1. Description of underlying health problem

Chronic hepatitis C is a slowly progressive disease of the liver caused by the hepatitis C virus. Generally, the virus is transmitted parenterally but the natural history of the disease is not completely understood. It is acquired through intravenous drug use and the sharing of needles. HCV was spread through the use of contaminated blood products prior to the introduction of a heat inactivation step in 1986 and prior to the introduction of blood screening in 1991[1;2] HCV was spread through blood transfusions. There is also a small risk associated with tattooing, electrolysis, ear-piercing and acupuncture[1]. Sexual infection and transmission from mother to child can also occur[1]. Concomitant HIV infection is thought to increase the risk of transmission[2]. The risk of transmission from a patient with HCV by needle stick injury to a healthcare worker is about 1 in 30 (1 in 3 for hepatitis B and 1 in 300 for HIV).

After exposure, patients are often asymptomatic but about 20% will develop an acute hepatitis, some of whom will experience malaise, weakness and anorexia. Up to 85% of those exposed fail to clear the virus and go on to develop chronic hepatitis[3], although it has been suggested that this might be an over-estimate (See Appendix 1 for a review of natural history studies). This is attributed to its genetic diversity, which prevents the immune system mounting an effective response. Chronic disease can be distinguished by mild necro-inflammatory activity in the liver, with no or minimal fibrosis, or more severe disease with fibrosis and in patients with very advanced disease cirrhosis, liver failure and hepatocellular carcinoma.

The rate of progression of the disease is slow and variable, over 20-50 years. About 20-30% of those initially infected develop cirrhosis within 20 years[2-4] and 1-4% of these are at high risk of hepatocellular

carcinoma[5]. A third may never progress to cirrhosis or will not progress for at least 50 years[4]. Patients often do not become symptomatic until liver disease is advanced. Some patients with end stage liver disease or hepatocellular carcinoma may require liver transplantation.

Seef (2002) [6] reviewed the risk factors associated with disease progression. There is some evidence to suggest a lower rate of progression amongst women, and also a lower progression to cirrhosis among African Americans in comparison to Caucasians. Co-infection with HIV is also associated with more rapid progression of hepatitis C. Genotype, however, is not thought to be associated with progression. Obesity also appears to increase the risk of progression[7].

External factors associated with progression include excessive alcohol consumption, and is it suspected that smoking may play a role, although there is little evidence to confirm this yet. A likely confounder is the fact that many people who smoke also consume alcohol, sometimes excessively, thus making it difficult to assess the independent effect of tobacco. Data also suggest that the younger the age at infection, the slower the rate of progression. Infection at a 'younger' age (i.e. <40 years) progresses so that 20 years after acute infection cirrhosis will have developed in 2%-8% of individuals. In contrast, 20% of patients infected at an 'older' age (i.e. >40 years) will be cirrhotic within 20 years. Poynard *et al.* (2001) [8] found that fibrosis progression was greatest after the age of 50, and is related to age at infection. For example, major acceleration could occur 10 years after infection at age 50, or 40 years after infection at age 10. This underscores the importance of treating patients with anti-viral therapy as early as possible.

2.2 Incidence and prevalence

It is believed that 100-170 million people worldwide are infected with hepatitis C. In a population survey conducted in the United States the prevalence was much higher at 1.8% (approximately 4 million people) [9], and the Centers for Disease Control estimated that the disease causes 8000 to 10,000 deaths each year[5] in the USA.

The prevalence in the United Kingdom is uncertain, but estimated to be between 0.1% and 1%. In Scotland prevalence is estimated to be 0.6%, the majority of whom are injecting drug users. Between 1992 and 1996 a total of 5232 reports of HCV infection were received from laboratories in England and Wales[10]. The majority, 38%, were in the 35-34 age group, with 27% in the 35-44 age group, and males more than twice as likely to be infected than females. Data from the Trent HCV Study group show that the total number of anti-HCV positive patients recorded in the region (assumed total population of 5.12 million) between 1991 and 1998 was 2546, representing a population-based prevalence of 0.05%[11]. These figures should be treated with caution, since they come from population-based reporting of positive tests, and there will be other

patients who are asymptomatic and who have not been tested. Public Health Laboratory Service (PHLS) data show that prevalence in specific groups is higher – 0.2% (Northern and Yorkshire) to 0.4% (London) in antenatal clinic attenders; 1.07% in Genito Urinary Medicine (GUM) clinic attenders, but with a higher rate in London (2.75%) than elsewhere (under 1%), which can be explained by the prevalence of drug use. The prevalence was 37% amongst injecting drug users (IDUs), 0.07% after excluding them. Prevalence is estimated as 0.06% in new blood donors, 0.2 to 0.4% in antenatal clinic attenders (varying amongst regions), 0.72% in organ donors[12] and amongst injecting drug users it is reported to be 60-85%[13]. The numbers of notifications to the Communicable Disease Surveillance Centre (CDSC) has risen from a few hundred a year in the early 1990s to over 5,000 a year now. However the number of new cases detected through the testing of residual samples in microbiological laboratories has varied from 1.07% in 1986; 0.55% in 1991 and 0.70% in 1996, suggesting that there may have been a peak of infection before the mid-eighties. Viral inactivation of blood products such as clotting factors started in 1985, but drug abuse might be the likeliest cause, with a mid-eighties peak of hepatitis B infection amongst IDUs, which may be a marker for hepatitis C spread as well.

There are up to 11 different genotypes of hepatitis C virus, the prevalence of which varies geographically. Genotype 1a is common in North and South America, and Australia, whilst 1b is mostly found in Europe and Asia. Genotype 2a is common in Japan and China, 2b is prevalent in the US and Northern Europe, 3a is highly prevalent in Australia and South Asia, whilst 4 is commonly found in Egypt and central Africa. In England and Wales the most prevalent genotypes are 3a (37%), 1a (32%) and 1b (15%)[14]. In general, genotypes 1a, 1b and 4 respond less favourably to interferon treatment in comparison to other genotypes. There are variations by the source of infection, with type 1 more common (60%) in haemophiliacs than type 3, which is the most common type in IDUs (47% type 1 and 43% type 3). This means that those infected with blood products may respond less well to treatment than those who acquired the virus through drug abuse.

Treatment is regarded as successful if blood tests indicating inflammatory liver damage (alanine aminotransferase) return to normal and if the hepatitis C virus disappears from the blood. A complete response is defined as acceptable ALT levels and no detectable HCV RNA at the end of treatment, and a sustained response constitutes maintenance of these levels for at least six months after the treatment has stopped. Early studies used ALT levels and liver histology as outcome measures; later trials added disappearance of the virus, once it could be measured. It is assumed that such measurements indicate response to treatment and if patients respond this will prevent progression of liver disease and development of cirrhosis, portal hypertension, liver failure and possible hepatocellular carcinoma[15]. Those patients with long-term remission and loss of the virus are

thought to be unlikely to develop cirrhosis or liver cancer[16]. It is recognised that the outcomes used are surrogate markers but it is still unclear whether a sustained response improves the long-term prognosis for these patients or if this represents a cure. A recent cohort of 80 patients who had sustained a response to interferon alpha have been followed for up to six years. Response to treatment was maintained and liver histology improved in more than 90% of patients[17].

2.3 Health-related quality of life in hepatitis C patients

As many patients do not display symptoms, the burden of ill-health for patients with chronic hepatitis C is not thought to be great. However, non-specific symptoms including fatigue, irritability, depression, nausea, headache, muscle ache, anorexia, abdominal discomfort, and right upper quadrant pain have been reported[18-20]. There is also some preliminary evidence to suggest cognitive impairment in patients with mild disease, a so-called 'brain fog'[21;22].

The general perception that chronic HCV infection is an asymptomatic disease having a marginal impact on a patient's health-related quality of life (HRQOL) has been challenged by a number of studies in recent years. Studies evaluating the HRQOL in HCV patients have relied on the 36-item short-form health survey (SF-36). Derived from the Medical Outcomes Survey, the survey instrument comprises 8 sub-scales, which evaluate the degree of impairment from a patient's ideal state of health[23]. The SF-36 is generally supplemented with several disease-specific scales to characterise particular problems experienced by patients (e.g., health distress, limitations caused by HCV infection) [18].

Reductions in HRQOL for HCV patients are suggested to be clinically and socially relevant[24]. A study which examined the HRQOL of patients with chronic hepatitis C found that these patients scored significantly lower on all sub-scales of the SF-36 in comparison to population norms. The disease that was analogous to the HRQOL of the HCV group was type II diabetes, although chronic HCV patients scored significantly lower than diabetes patients on the vitality, social functioning and bodily pain SF-36 sub-scales[25]. These results have been confirmed in two recent studies where chronic HCV patients again scored significantly lower on all SF-36 sub-scales in comparison to both a UK healthy control population and healthy controls in the United States[24]. Furthermore, significant reductions in HRQOL have been shown to occur in patients with mild HCV[21]and for chronic HCV patients who do not have cirrhosis or a history of injecting drug use[26].

The causes of impaired HRQOL and the aetiology of extrahepatic symptoms in patients with HCV are poorly understood[22]. Patients with psychiatric disorders are reported to have a higher prevalence of hepatitis C, and psychiatric symptoms and emotional distress appear to be more common among hepatitis C patients than in the general population[27]. In a recent study of 220 patients not selected for anti-viral

therapy which aimed to determine the prevalence, type and severity of psychological symptoms, clinically significant emotional distress was detected in 35% of the study population (N.B a history of alcoholism and intravaenous drug use was not associated with emotional distress) [27]. This figure is much larger than that found in population controls (10%) and compares to that seen in asymptomatic people with HIV infection and rheumatoid arthritis. Significantly elevated scores for depression, anxiety, somatization, psychoticism, and obsessive-compulsive disorders were found in 28-40% of patients. Psychiatric and medical co-morbidities (defined as active problems requiring treatment and/or monitoring) were identified in 71% of patients. There was also a significant correlation between elevated emotional distress (Global Severity Index scores) and lower HRQOL (SF-36) scores. It was also found that patients who expected not to survive because of their illness had the highest psychiatric distress scores. This study therefore underscores the significant relationship between hepatitis C, HRQOL and poor mental health, and the need for further investigation into the mechanisms between them.

Clinicians point out that patients' awareness that they carry a transmissible disease and the perceived risk of passing the disease to others can also significantly affect their quality of life. Although this psychological effect has not be specifically evaluated, it is a major motivator for patients to seek treatment.

Successful eradication of hepatitis C has been demonstrated to improve patients' HRQOL. HCV patients who respond to interferon alpha monotherapy (biological and virological sustained responders) have significantly greater improvement in HRQOL than patients who do not respond to treatment[24;28;29] (although it is suggested that HRQOL scores of sustained responders remain slightly lower than population controls[27]). Improvements are primarily related to the SF-36 sub-scales of perception of general health, vitality and social functioning, and to disease-specific scales concerning feelings of health distress and limitations caused by HCV infection[24;28]. Treatment with interferon monotherapy causes an overall decrease in HRQOL scores from baseline during therapy, returning to pre-treatment levels at the cessation of therapy[28;30]. Although the HRQOL of patients whilst receiving dual therapy with interferon and ribavirin decreased slightly more than monotherapy patients during treatment, patients receiving dual therapy exhibited greater improvements in vitality, social functioning, health distress and general health than monotherapy patients at the end of treatment[30]. This raises the question of whether the pegylated interferon is likely to result in greater HRQOL benefits at the end of treatment in comparison to non-pegylated interferon.

Increases in HRQOL due to successful treatment have been suggested to equate to meaningful improvements in the performance of daily activities and lower rates of tiredness and concern regarding hepatitis infection[28]. This may be predictive of a reduced demand for healthcare

services and an increase in productivity in the workplace for these individuals[30]. Hence although the usual purpose of treatment is to prevent progression to more serious liver disease, in some patients it is worthwhile in terms of symptom relief and quality of life alone. This raises another issue, the extent to which patients with mild chronic hepatitis C experience better HRQOL as the result of anti-viral therapy. If this can be demonstrated it would provide a stronger argument for treating all patients with mild disease. This issue is being investigated by the UK HTA Programme funded randomised controlled trial (RCT) of antiviral therapy (IFN + RBV vs IFN) in patients with mild hepatitis C (see section 3.6). The trial is using the SF-36 instrument (including a validated hepatitis C disease specific module) to measure changes in HRQOL before, during and after treatment. Patients will also complete a socio-economic questionnaire before and after treatment.

2.4 Current service provision

Until several years ago, patients with moderate to severe chronic hepatitis C were treated with interferon alpha ("Intron A", Schering-Plough; "Roferon A", Roche) via subcutaneous injection around three times a week, but only around 17% of patients achieved a sustained virological response[31]. Dual therapy consisting of interferon alpha 2 with the oral anti-viral drug ribavirin ("Rebetol", Schering-Plough; "Virazole", ICN) led to response rates of 41% in patients not previously treated with interferon[32] and 49% in those who had relapsed following previous interferon treatment[33], and gained a licence in 1999.

On the basis of these landmark trials dual therapy replaced monotherapy as the treatment of choice in patients with hepatitis C. However, Foster and Chapman (2000) [34] writing in the BMJ just prior to the publication of NICE guidance on this issue noted that, on the basis of a postal survey of 447 clinicians of whom 80 (18%) replied, adequate funding for dual therapy was only available in a minority of health districts suggesting 'postcode prescribing'. For example, only around a third of respondents indicated that their health authority had a budget for dual therapy.

In October 2000 NICE issued guidance on treatment for chronic hepatitis C, based on an assessment report[35], recommending dual therapy with interferon alpha and ribavirin for the treatment of moderate to severe hepatitis C (defined as histological evidence of significant scarring (fibrosis) and/or significant necrotic inflammation), at standard doses for patients over the age of 18 years[36]. For patients not previously treated with interferon ('treatment naïve' patients) and those who have relapsed following previous therapy, six months treatment was recommended. A further six months therapy was recommended only for patients infected with genotype 1 who have had an initial response by six months.

Clinical guidelines for the management of hepatitis C have also been published by the Royal College of Physicians of London and the British Society of Gastroenterology[37]. These were published in 2001 and include evidence-based information on the background of the disease, diagnosis, and treatment. At the time of publication, little information was available on the efficacy of PEG and therefore the guidelines concluded that there were insufficient data to evaluate the role of pegylated interferon compared with other interferons, but that once trials were published the guidelines would be reassessed.

These clinical guidelines are consistent with the existing NICE guidance on treatment for hepatitis C. Using the evidence available, both sets of recommendations suggest that interferon (IFN) and ribavirin (RBV) dual therapy is the treatment of choice for patients who had not previously been treated or for those who had been treated with IFN monotherapy and relapsed. The recommendations differ slightly in the durations of treatment recommended for patients with genotype 1 infection. The NICE guidance recommends that these patients should be treated for 6 months and for an additional 6 months only in those who become clear of HCV-RNA within the first 6 months. The Royal College guidelines recommend 6 months of treatment for patients with genotype 1 and low levels of infection (< 2 million copies/ml) and 12 months of treatment in patients with genotype 1 and high levels of infection (>2 million copies/ml) or cases in which HCV quantitation is not available.

The Royal College guidelines recommend liver biopsy for patients found to be viraemic whether or not liver function tests are abnormal. Liver biopsy is valuable for assessing the status of liver inflammation, potential progression of fibrosis, and the presence or absence of cirrhosis. Biopsy is recommended for these assessments and to assess suitability for treatment.

The guidelines also acknowledge that there is disagreement about the treatment of patients with mild disease. On the basis of relatively low quality evidence they conclude that treatment can reasonably be withheld in patients with mild disease but they should be followed to determine if there is progressive liver disease by the use of repeated biopsy after every 2-3 years or if there is a significant change in liver function tests that is 2-3 times normal levels.

2.5 Description of new intervention

2.5.1 Pegylated interferon for previously untreated patients

Since the NICE guidance was issued there has been increasing interest in the use of 'pegylated' interferon[38]. "Pegylation" involves the addition of polyethylene glycol (PEG) molecules to the interferon alpha active molecule via either linear or branched chains. It is a method for ensuring delayed renal clearance of the drug, thus prolonging action, necessitating fewer doses and resulting in greater efficacy. Pegylated

interferon can therefore be given (by subcutaneous injection) once a week rather than three times a week as for interferon alpha, thus being more convenient for the patient and potentially lessening the likelihood of non-compliance. Products have been developed by Roche (2a "Pegasys") and by Schering-Plough (2b "ViraferonPeg"). The indication is for the treatment of adult patients (both those who are interferon naïve, and those who have relapsed following previous treatment) with histologically proven chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti HCV. Pegylated interferon can be combined with ribavirin, or as monotherapy if ribavirin is contra-indicated[39].

Dose ranging studies have established 180 micrograms (mcg) weekly as being the average optimum dose for pegylated interferon 2a[40] and 1.5 mcg/kg weekly the recommended dose for pegylated interferon 2b. It has been shown that adjusting the dose of 2b according to body weight optimises sustained virological response rates[41].

Attention has turned to the combination of pegylated interferon and ribavirin as a potential replacement for dual therapy with interferon alpha and ribavirin. However, pegylated interferon is more expensive. There may be some off-setting savings both in the shorter term (from the reduced frequency of injections) and in the longer term.

Although dual therapy with non-pegylated interferon is the current treatment of choice, anecdotal evidence suggests that pegylated interferon is routinely used in some areas. In 2002, the Scottish Medicines Consortium advised that pegylated interferon alpha-2b was an appropriate treatment for adults with chronic hepatitis C.[42]

In 2000 the US National Institutes of Health (NIH) recommended pegylated interferon for the initial treatment of previously untreated patients with chronic hepatitis C[43]. In 2002 an NIH consensus conference recommended that genotype 1 patients be treated with pegylated interferon (2b) dual therapy for 48 weeks, and patients with genotypes 2 and 3 be treated for only 24 weeks but a lower dose of ribavirin (800mg per day)[44]. It is also recommended that assessment of viral response should be routine in patients with genotype 1, and those who do not achieve a viral response after 12 weeks should discontinue treatment.

2.5.2 Re-treatment of non-responders to interferon alpha monotherapy

Another important issue is the clinical-effectiveness and cost-effectiveness of re-treating patients who failed to respond (i.e. do not become HCV RNA negative) to interferon monotherapy, the one time standard treatment. It is not clear how many patients in England and Wales fit into this category although Cammà *et al.* (2002) [45] suggest that worldwide 'a large cohort of IFN monotherapy non-responders still

exists within the pool of subjects with chronic hepatitis C' (p. 864). A Cochrane systematic review of re-treatment with another course of IFN monotherapy found that only around 17% patients achieved a SVR, with 48 weeks of treatment more effective than 24 weeks[46]. Given that dual therapy with interferon and ribavirin has succeeded interferon monotherapy as the standard treatment in recent years, it seems unlikely that many patients would now be given monotherapy unless intolerant to ribavirin. However, there is no guidance from NICE for such patients. With the introduction of pegylated interferon it is also likely that these patients may be re-treated with dual therapy with PEG as opposed to dual therapy with IFN. However, it is unlikely that at this stage there will be much evidence relating to re-treatment using PEG dual therapy.

One of the aims of this review is therefore to assess the clinical-effectiveness and cost-effectiveness of re-treating patients who have failed to respond to a previous course of IFN monotherapy. Re-treatment strategies include dual therapy with pegylated interferon and ribavirin (where evidence is available), and re-treatment with non-pegylated interferon and ribavirin.

2.6 Mild chronic hepatitis C and the need for biopsy

Standard practice at present is to perform liver biopsy before starting treatment, to assess severity of disease. Consensus is that patients with only mild liver disease should not be treated.

There are, however, a number of scenarios in which liver biopsy would not be required. The first would be if blood tests such as hyaluronic acid (HA) were a sufficiently good correlate of histology. There is some evidence to suggest that this might be the case. Serum HA was compared with conventional liver function tests including alanine aminotransferase (ALT), a-glutathione-S transferase (GST) and serum HCV RNA in a study of 130 patients with chronic hepatitis C in order to determine which identified the stage of liver fibrosis most accurately as assessed by liver biopsy[47]. Serum HA had a higher sensitivity and specificity than ALT and GST, suggesting it as a useful marker of liver fibrosis. However, use of such tests assumes that treatment is dependent on severity of liver changes, and there would be less justification for biopsy in patients in whom treatment was being considered because of systemic symptoms - the biopsy need not be done if it was decided to treat the symptoms. The clinical-effectiveness and cost-effectiveness of non-invasive tests compared with liver biopsy will be examined, where evidence is available.

The second scenario would be if it were demonstrated that treating patients with mild disease was cost-effective. An HTA funded RCT of dual therapy (interferon alpha and ribavirin) in patients with mild chronic hepatitis C is currently in progress and is due for completion around mid 2003. If this trial showed that it was of benefit in those

patients (either in terms of preventing long-term complications or in improving immediate quality of life), the need for biopsy would again be reduced.

There are occasional deaths after biopsy, but an audit in England and Wales found a death rate of between 0.13% and 0.33%[48]. The complication rate, as indicated by bleeding after biopsy, was lower (by about two-thirds) in those whose biopsies were done by more experienced operators, and this was more common in gastroenterological patients (compared with general medical ones). Patients with hepatitis C are more likely to be cared for in specialist centres and to have a complication rate lower than the average in the audit. There has been, however, an uncertainty about treating patients with mild disease because we do not fully know the natural history in this patient group, and hence precisely what we are preventing with treatment. Expert opinion suggests that some clinicians may be reluctant to treat those with minimal symptoms due to uncertainty regarding whether they derive substantial benefit. However, it might be cost-effective to treat this group, even if only a proportion go on to develop more aggressive disease, because others may have symptoms due to hepatic or extra-hepatic disease which would improve after treatment.

The third scenario is the treatment of patients with genotypes 2 and 3 regardless of histology. Sustained virological response rates for these patients treated with pegylated interferon dual therapy reached between 75-80%[41;49] (see section 3.2.2) [49]. Consequently support for treating these patients without biopsy is gaining ground amongst clinicians. Furthermore, French guidelines also suggest these patients do not need a biopsy.

The fourth scenario would be if it were shown that treatment was indicated early after infection, in which case patients would be treated before the severity of future liver disease could be known. A recent study of 24 weeks treatment with interferon alpha monotherapy in 44 patients known or suspected to have been exposed to HCV in the previous 4 months showed encouraging results[50] (see section 3.8).

3. Effectiveness

3.1 Methods for reviewing effectiveness

3.1.1 Inclusion criteria

The following inclusion criteria, as specified in the study protocol, were set (see Appendix 3 for the inclusion worksheet used):

Interventions:

- Dual therapy (pegylated interferon alpha and ribavirin) versus dual therapy (interferon alpha and ribavirin)
- Monotherapy (pegylated interferon alpha) versus monotherapy (interferon alpha)

Patients:

- For the primary research question on the effectiveness of pegylated interferon treatment the patient group were those with moderate to severe chronic hepatitis C infection not previously treated with interferon alpha.
- The protocol for the review also mentions the possible extension of the scope to include patients with chronic mild disease. However, results of a key trial of anti-viral therapy in mild disease are not yet available. Consequently, the focus is primarily on patients with more advanced disease. However, Section 3.6 provides a brief summary of the current evidence in this area.
- For the secondary research question on re-treatment, the patients of interest were those who had previously failed interferon alpha monotherapy and were being re-treated with dual therapy (interferon alpha and ribavirin).
- Patients with acute hepatitis C were not included in the current report, however, a brief summary of evidence for the effectiveness of anti-viral treatment in this area is provided in section 3.8.

Outcome measures (for clinical-effectiveness studies):

- Sustained clearance of infection, as shown by absence of viral RNA 6 months or longer after the end of treatment;
- Adverse effects of treatment

Study types:

- Clinical-effectiveness of treatment:
  - systematic reviews (including meta-analyses) of randomised controlled trials (RCTs); and Phase III RCTs;
- Cost-effectiveness:
  - cost-effectiveness/cost-utility studies; quality of life studies;

Publication status:

- Fully published peer-reviewed reports/articles were used for primary analysis.
- Unpublished material (including conference abstracts) were used primarily for background information and context. Where relevant, studies reported in conference abstract form are summarised in the current report but their results are not used in economic modelling (although they potentially could be used in sensitivity analysis), or to support conclusions or recommendations. Caveats are included to urge caution in the interpretation of such material. See Appendix 4 for a table of conference abstracts of pegylated interferon treatment.
- Material supplied as academic or commercial in confidence is underlined in the current report.

Language:

- Only English language articles were included

3.1.2 Literature searching

A sensitive search strategy was developed, tested, and refined by an information scientist in order to capture the range of relevant study types (see Appendix 2 for search strategy). The strategy was applied to the following electronic bibliographic databases:

- Medline (Silverplatter)
- Pre-Medline (PubMed)
- Embase (Silverplatter)
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Controlled Trials Register (CCTR)
- BIOSIS
- Web of Science Proceedings
- Science Citation Index (SCI)
- Database of Abstracts of Reviews (DARE)
- NHS CRD HTA database (University of York)
- NHS Economic Evaluation Database (NEED)
- National Research Register (NRR)

Searches were run for the period 2000 to August/September 2002. In March 2003 these were repeated to identify any studies published since September 2002. Searching for studies of re-treatment to interferon monotherapy followed a slightly different method and full details are provided in section 3.3.

Contact was made with experts in the field to identify relevant trials, and internet sites listing details of current controlled trials and those dealing with hepatitis and liver disease were also searched. The submissions to NICE from the drug companies were also used as a method of identifying relevant studies.

References to studies identified through literature searching were downloaded into Reference Manager software. Inclusion criteria were applied to titles and abstracts and, where necessary, full reports were retrieved for further inspection. A keywording classification system for the database was devised, tested, and refined. The purpose was to facilitate efficient retrieval from the database of relevant studies. A keyword was applied to each record in the database to indicate whether it was to be included or excluded. Further keywords were applied to included studies to indicate study type (e.g. clinical-effectiveness; cost-effectiveness; epidemiology etc). Clinical-effectiveness studies were further classified according to the nature of the intervention (e.g. PEG dual therapy); the study type (e.g. RCT); and whether or not any additional relevant information was provided (e.g. an integral cost-effectiveness analysis).

3.1.3 Data extraction and critical appraisal

Included clinical-effectiveness studies of pegylated interferon treatment underwent detailed data extraction to a standardised template. Studies were also critically appraised using criteria devised by the NHS Centre for Reviews and Dissemination (NHS CRD) (see Appendix 5). Extraction and appraisal were performed by one reviewer and checked by a second with disagreements resolved through discussion.

3.1.4 Methods of analysis/synthesis

Both qualitative and quantitative approaches were employed to synthesise the results of the RCTs. Data extraction tables were used to compile a narrative summary of the main characteristics and results of the trials. In addition, a meta-analysis was performed with Cochrane Review Manager Software (Version 4.1) using a random effects model. 'Confidence Interval Analysis' software (Version 0.2, © Gardner, 1989) was used to compute confidence intervals where not provided by study authors.

3.2. Results – Clinical-effectiveness of anti-viral therapy

3.2.1. Quantity and quality of research available

Initial literature searching generated a total of 637 'hits' (i.e. references to studies). As the review progressed 198 references were added to the database most of which had been identified through searching reference lists of papers already retrieved. At the end of March 2003 the original literature search was repeated to identify studies published since the original search. A further 159 references were added to the database, bringing the grand total of articles identified to 996.

A total of 6 fully published RCTs of the effectiveness of pegylated interferon treatment met the inclusion criteria for this review (Please refer to section 3.5 for full details of the number of re-treatment studies identified).

Design

The number of participants in the six RCTs varied considerably in size ranging from 159 to 1530. Five were parallel group designs whilst the sixth[40] randomised three separate cohorts either to IFN or to successively higher doses of PEG. This design was used in order to examine the safety of each PEG dose before using higher doses.

Two trials evaluated the effectiveness of dual therapy (PEG + RBV[41;49], see Table 1). One of these trials used PEG α-2b and IFN α-2b[41] whereas the other used PEG α-2a and IFN α-2a[49]. The Manns *et al.* [41] trial used a design in which the manipulation of the dosing of PEG α-2b and RBV were confounded. The two arms combining PEG and RBV were compared with an arm combining IFN and RBV. The Fried *et al.* trial[49] compared the same dose of PEG α-2a with and without RBV against IFN plus RBV.

Table 1 Characteristics of included RCTs of combination therapy

Author	Study ID / Sponsor	Number of Participants	Arm 1	Arm 2	Arm 3
Manns *et al.* (2002) [41]	C/98-580 (Schering-Plough)	1530	PEG IFN α-2b, 1.5 µg/kg/wk + RBV 800 mg/day n=511	PEG IFN α-2b, 1.5 µg/kg/wk for 4 wk then 0.5 µg/kg/wk for 44 wk + RBV 1000-1200 mg/day n=514	IFN α-2b, 3 MIU 3x/wk + RBV 1000-1200 mg/day n=505
Fried *et al.* (2002) [49]	(NV15801) (Hoffman-La Roche)	1121	PEG IFN α-2a, 180 µg/wk + RBV 1000-1200 mg/day n=453	PEG IFN α-2a, 180 µg/wk + placebo n=224	IFN α-2a, 3 MIU 3x/wk + RBV 1000-1200 mg/day n=444

Four trials tested monotherapy with PEG against monotherapy using IFN (see Table 2). One of these trials tested PEG α-2b against IFN α-2b[51] whereas the others tested PEG α-2a against IFN α-2a. One trial[40] tested small groups of participants on 4 different doses of PEG α-2a versus IFN α-2a. Another tested three doses of PEG α-2b against IFN α-2b[51]. A third tested two doses of PEG α-2a against IFN α-2a. [52] The remaining trial tested one dose of PEG α-2a against IFN α-2a.

The two trials that tested PEG α-2b both applied doses of PEG and the comparator IFN according to body weight. The trials that used PEG and IFN α-2a administered fixed doses of PEG and IFN.

Both of the dual therapy trials included arms in which the dose of RBV was administered according to body weight with patients who weighed ≤ 75 kg receiving 1000 mg/day and those weighing > 75 kg receiving 1200 mg/day. The Manns *et al*[41] trial included one arm in which the RBV dose combined with PEG α-2b was

Table 2 Characteristics of included RCTs of monotherapy

Author	Study ID / Sponsor	Number of Participants	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Heathcote *et al.* (2000) [52]	NV 15495 (Hoffman-La Roche)	271	PEG IFNα-2a, 90 µg/wk n = 96	PEG IFN α-2a, 180 µg/wk n = 87	IFN α-2a, 3 MIU 3x/wk n=88		
Zeuzem *et al.*	NV 15497 (Hoffman-	531	PEG IFN α-2a, 180	IFN α-2a,			

(2000) [53]	La Roche)		µg/wk n=267	6MIU 3x/wk for 12 wk then 3MIU 3x/wk for 36 wk n=264			
Lindsay *et al.* (2001) [51]	C/197-010 (Schering-Plough)	1219	PEG IFNα-2b, 0.5 µg/kg/wk n=315	PEG IFN α-2b, 1.0 µg/kg/wk n=297	PEG IFN α-2b, 1.5 µg/kg/wk n=304	IFN α-2b, 3MIU 3x/wk n=303	
Reddy *et al.* (2001) [40]	Hoffman-La Roche	159	PEG IFN α-2a, 45µg/wk n = 20	PEG IFN α-2a, 90 µg/wk n=20	PEG IFN α-2a, 180 µg/wk n=45	PEG IFN α-2a, 270 µg/wk n=41	IFN α-2a, 3MIU 3x/wk n=33

fixed at 800 mg/day and one arm in which the RBV dose was administered according to weight as above.

All six trials administered the study interventions for 48 weeks with a follow-up interval of 24 weeks (final evaluation at 72 weeks from inception). There was general uniformity in the choice of outcome measures across the trials. The primary outcome in every trial was sustained virological response (SVR) at follow-up (72 wk). In all trials the SVR was defined as undetectable levels of HCV RNA at follow-up. In four trials plasma HCV RNA levels were evaluated using the Cobas Amplicor HCV test (version 2.0) with a lower limit of detection of 100 copies/ml. In one trial[51] a different PCR assay (National Genetics Institute) with the same lower detection limit was used. In the remaining trial[40] an earlier version of the HCV RNA test was used with a detection limit of 2,000 copies/ml, but samples at follow-up that had undetectable levels of HCV RNA were retested with the more sensitive test. All trials also reported virological response at end of treatment (48 wk). Some trials reported virological responses at earlier time points (e.g. after 12 weeks of treatment, see sections 3.2.2 and 3.2.3) as well as correlations between baseline characteristics and/or early viral response and SVR.

Other outcomes included biochemical response (ALT levels), histological response (e.g. liver biopsy), and adverse effects and laboratory abnormalities. Each of the trials reporting histological responses used the same system for grading histological response. The Knodell Histology Activity Index was used. This Index produces scores ranging from 0 to 22 with 18 points for inflammation (0 = none, 18 = severe) and 4 points for fibrosis (0 = none, 4 cirrhosis). In each case, a histological response was defined as a decrease in HAI score of ≥ 2 units. In two trials [41;51] changes in inflammation and fibrosis were reported separately with fibrosis score changes of ≥ 1 unit defined as improvement or worsening.

Methodological quality

The trials were similar in methodological characteristics (see Appendix 6). In general, trials were of good quality, although reporting of methodological details could have been more thorough. For example, only one trial[52] explicitly reported a randomisation procedure that assured true random assignment, and only one trial[41] explicitly reported allocation concealment. In most cases, groups appeared similar at baseline in important demographic and prognostic characteristics, although in some cases supporting statistical comparisons were not provided. In two trials[40;51] there were baseline differences that might have affected results (see Table 3). Given the different timing of administration of PEG and IFN (once per week versus 3 times per week, respectively) most of the trials were open label. In one trial that manipulated the addition of RBV or placebo to PEG there was double blinding as to whether participants were receiving RBV or placebo. Pathologists who evaluated liver histology were always blinded as to treatment status and assays were generally said to be conducted at central laboratories although there was often not specific mention of blinding of these assessors. All trials performed an intention to treat analysis for the primary outcome of SVR. In Fried *et al's* trial, the last observed HCV RNA level was used in assessment of efficacy for patients with at least 20 wks of follow-up. All patients with follow-up of less than 20 weeks were considered to have had no response to treatment. In Zeuzem *et al's* trial patients not present at 72 week assessment were classed as non-responders at that point. For safety analyses, it was generally the case that all patients who had received at least one dose of study medication were included in the analysis.

Relatively high numbers of patients withdrew from trials (approximately 20-30%) because of adverse effects or other reasons. There was variation in the detailed reporting of numbers of patients withdrawing and losses to follow-up and reasons for losses. Only two trials[41;53] reported conducting a power analysis to determine the optimum sample size necessary.

Participant inclusion/exclusion criteria

The inclusion and exclusion criteria for all six trials were broadly similar. All included adult patients with chronic hepatitis C who had

not received previous treatment with IFN. Four[41;49;51;52] of the six required a liver biopsy consistent with chronic hepatitis C (most within the previous year). The same four trials specified that HCV RNA must be detectable in serum. Five[41;49;51-53] specified that serum ALT levels should be elevated. Most of these required at least 2 elevated serum ALT readings within six months before entry into the trial.

Most trials reported excluding participants who had various co-morbidities. Two trials reported excluding patients with 'substantial co-existing conditions'[49] or conditions that would 'interfere with participation'[51]. Other conditions were specific exclusion criteria. Five trials specifically excluded patients with HIV infection and the sixth[40] excluded patients on immunomodulatory, antiviral or investigational compounds, which would seem to effectively exclude patients with HIV among others. Other causes of liver disease excluded participants in 4 trials[40;41;51;52]. Patients with decompensated cirrhosis[41;52] or decompensated liver disease[49;53] were also generally excluded. Most trials excluded participants with co-morbidities such as: psychiatric disorders[40;41;49;52;53], seizure disorder[40;41;52;53], cardiovascular disease[40;41;52;53], retinopathy[40;52;53], or cancer/neoplastic disease[40;52;53]. Two trials[41;51] excluded patients with haemophilia or haemoglobinopathies. Two trials excluded patients with autoimmune disorders[41;53].

All trials had certain laboratory readings that were required. All excluded patients with thrombocytopenia; requiring platelet counts ranging from > 75,000/mm^3 to >130,000/mm^3. Five[41;49;51-53] excluded patients with low neutrophil counts with the minimum required ranging from 1500 – 1800 mm^3. Three [41;49;51] excluded patients with anaemia who had haemoglobin <12gm/dL for females and < 13 gm/dL for males. Three[40;41;51] excluded patients with low white blood counts ranging from 1500/mm^3 to 4000/mm^3. Four[41;51-53] excluded patients with abnormal alpha fetoprotein levels with exclusion thresholds ranging from > 25 ng/mL to 100 ng/mL. Four[40;41;49;53] required serum creatinine within normal limits or excluded patients with levels > 1.5 times the upper limit of normal.

Other exclusion criteria included substance abuse[40;49;51], pregnancy or breastfeeding[40;51], or inability or unwillingness to use contraception[41;53].

Participant Characteristics

The trials were broadly similar in their participant samples with two exceptions (see Table 3). The Heathcote *et al.* [52] trial specifically recruited patients with biopsy-proven cirrhosis (78%) or bridging fibrosis (21%) whereas the other trials, when reported, specifically excluded patients with bridging fibrosis or cirrhosis or recruited relatively few patients with bridging fibrosis or cirrhosis (approximately 10-15% of participants). The other difference among trials was the baseline viral load. In three trials the average baseline viral load was

over 6 million copies/ml[49;52;53] whereas in the remaining three trials the baseline viral load was less than 3.5 million copies/ml[40;41;51].

Generalisability to UK populations

The patient samples in the trials seem similar to patients with hepatitis C in England and Wales in some respects. The average age of participants in the 40s is consistent with a cohort of patients in the Trent region the bulk of whom were born between 1950 and 1969[11]. This cohort was also found to have a male/female ratio of 2:1 which is similar to that in the trials. The trial participants were predominantly of genotype 1, which may not necessarily be similar to the distribution in the UK. Two reports suggest that genotype 3a may be the most common in England and Wales[14;54]. However, one of these reports[14] offers no data as to the representativeness of the sample from which these genotypes were assessed and the other[54] used only an antenatal sample. Another report[11] suggested that genotype 1 was most common, but excluded patients with haemophilia, HIV infection, or chronic renal failure.

Table 3 Baseline Characteristics of participants in included trials

Characteristic	**Dual therapy**		**Monotherapy**			
	Manns *et al.* (2002)[41]	**Fried *et al.* (2002)[49]**	**Heathcote *et al.* (2000)[52]**	**Zeuzem *et al.* (2000)[53]**	**Lindsay *et al.* (2001)[51]**	**Reddy *et al.* (2001)[40]**
Age	43.3	42.5	47.1	40	43	42
% Male /	66	71	72	69	63	79
% Genotypes						
1	68	64.9	56.5	62†	69.8†	73.6
1a	--	32.5	32.5	31	--	--
1b	--	30.8	24.0	31	--	--
1 other	--	1.6	--	--	--	--
2	29***	13.6	12.2	11	10.2	--
3	***	18	26.9	25	16.4	--
4	3	3	1.1	2	--	--
other	--	0.5	3.3	1	3.5*	23.9**
Baseline Viral Load	2.7	6.0	6.1	7.8	3.35	2.4
Ethnic Groups						
White	--	84.1	88.2	85	91	87
Asian/Oriental	--	5.7	2.6	9	--	1.3
Black	--	4.7	4.1	2	--	9
Other	--	5.4	5.2	3	--	2.5

-- = not reported
* = all genotypes other than 1-3 (thus may include patients with genotype 4)
** = all non-1 genotypes (NB. for 2.5% of patients genotype was missing)
***= genotypes 2 and 3
† = because of rounding percentages do not add up to 100%

This report found that 47% of hepatitis C patients were infected with genotype 1 and 39% with genotype 3. Regardless of the precise distribution, there is the suggestion that genotype 1 may be less prevalent in the UK population than in the trial samples. This may be important because past therapies have been least effective in patients with genotype 1 infection (see sections 3.2.2 and 3.2.3 for response rates of PEG according to genotype).

In summary, the patients included in the trials comprised a generally homogenous group of previously untreated patients, the majority male, white, in their 40s with genotype 1 and without significant co-morbidities.

3.2.2. Assessment of effectiveness in untreated patients - dual therapy (PEG + RBV)

Virological response

Table 4 shows the end of treatment and sustained virological response rates for the two RCTs. In both trials dual therapy with PEG was significantly more effective with a pooled end of treatment response rate of 67% (95% CI 64% - 69%) compared to 53% (95% CI 49% - 56%) for dual therapy with IFN + RBV. The pooled relative risk was 0.70 (95% CI 0.63-0.78) (Figure 1).

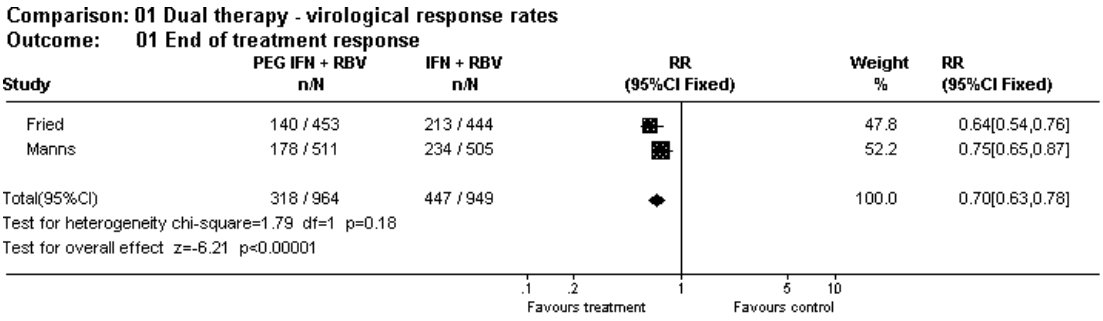
Table 4 Virological response rates for 48 weeks of dual therapy

Study	End of treatment response		End of follow-up response	
	PEG IFNα + RBV	IFNα + RBV	PEG IFNα + RBV	IFNα + RBV
Manns *et al.* (2002) [41]	65%*	54%	54%	47%
Fried *et al.* (2002) [49]	69%†	52%	56%	44%

* Statistically significant difference between groups ($p < 0.05$)

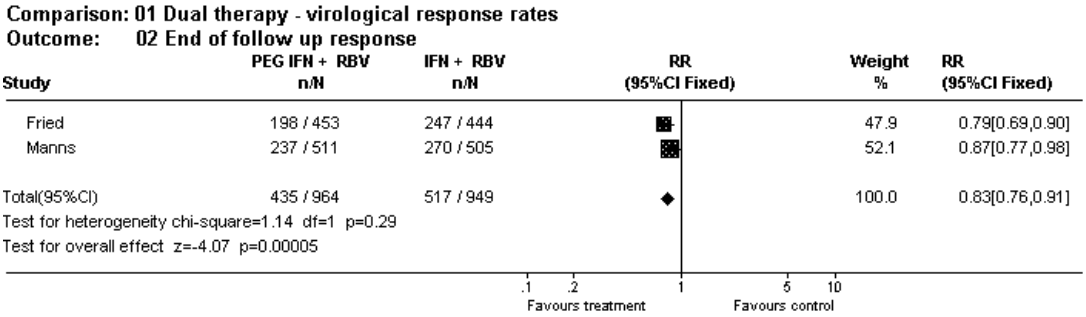
† Statistically significant difference between groups ($p \leq 0.01$)

Figure 1 Pooled Relative Risk (End of dual therapy)



The pooled sustained virological response rate was 55% (95% CI 52% - 58%), for dual therapy with PEG + RBV compared to 46% (95% CI 43%- 49%) for dual therapy with IFN + RBV, with a pooled relative risk of 0.83 (95% CI 0.76-0.91) (Figure 2).

Figure 2 Pooled Relative Risk (End of follow-up dual therapy)



Predictors of virological response – early response

Fried *et al*. (2000) reported 12 week data for the dual therapy arm of their trial, with a virological response rate of 86% (95% CI 83% - 89%). More common, however, was reporting of the proportion of patients who had achieved a response at week 12 who subsequently achieved a sustained response. In Fried *et al's* trial this proportion was 65%, whilst in Mann *et al's* trial the proportion of those who became HCV RNA negative for first time at 12 weeks and achieved SVR was 75% (with 32% HCV RNA negative for first time at week 24 achieving a SVR). Therefore up to three quarters of patients who had experienced a virological response after 12 weeks of therapy maintained their response at week 72. In Fried *et al's* trial 97% of patients who did not have an early virological response to dual therapy with PEG did not achieve a SVR.

The poor long term outcome for non-responders at 12 weeks has prompted the suggestion that therapy could potentially be stopped at this time for these patients. However, historically there has been no optimal definition of an 'early response' threshold. To this end Davis (2002) [55] pooled and analysed unpublished virological response data supplied by the sponsors of the trials by Manns *et al.* and Fried *et al.* to determine the optimal time for an early response.

Patients included in the analysis comprised 453 who received pegylated interferon 2a 180 µg combined with 1,000 – 1,200 mg of ribavirin, and 512 who were given pegylated interferon 2b 1.5 µg/kg weekly and 800mg ribavirin daily (Note that the analysis did not include patients who received non-pegylated interferon). Therefore, a total of 965 patients were analysed (n=446 / 67% with genotype 1; and n=277 / 29% with genotype 2 or 3). The definition of early response used was a fall in HCV RNA from baseline at week 12 of therapy (in the range of ≥ 3 to ≥ 1 $\log_{10}$ units) or to an undetectable level by qualitative PCR. Of the 965 treated patients 778 had an early virological response, of whom 526 (68%) went on to have a SVR, yielding a positive predictive value of 0.68. Of the 187 (19.4%) who did not have an EVR only 3 (1.6%) subsequently had a SVR, with a negative predictive value of 0.98. If treatment is stopped in the 19% of patients who do not achieve EVR at 12 weeks, only 0.6% of potential responders are missed. It was concluded that EVR is best defined as 'a fall in HCV RNA by at least 2

log_{10} units or to an undetectable level by a sensitive PCR after the first 12 weeks of treatment' (p. s150). The following recommendations were made:

- Patients with genotype 1 who achieve EVR at week 12 should complete the full 48 weeks of treatment. Those who do not achieve EVR should discontinue
- Patients with genotype 1 who achieve EVR but who are still HCV RNA positive at week 12 should be retested at week 24 using sensitive qualitative PCR. If still HCV RNA positive at week 24 then treatment should stop.
- Patients with genotype 2 or 3 should be treated for 24 weeks and need not have a 12 week assessment of EVR (given that all except one patient with these genotypes achieved an EVR).

Virological response according to prognostic factors

Both trials performed logistic regression analysis to examine the independent effect of a range of prognostic factors on sustained response, with broadly similar results. Factors such as age (≤ 40 years), body weight (≤ 75kg), and genotype (non-1) were significantly associated with SVR in both trials. In addition, sex, low baseline viral load (≤ 2 million copies per ml) and absence of bridging fibrosis/cirrhosis were also significantly associated with SVR in Manns *et al's* trial.

Table 5 shows the extent to which SVRs varied according to genotype. Across the genotypes patients treated with PEG + RBV dual therapy had higher response rates than those treated with dual therapy with IFN + RBV. However, there were some key differences between the two trials. Whilst patients with genotypes 2 and 3 did better on PEG dual therapy in the trial by Fried *et al.*, there was only a marginal difference for such patients in the trial by Manns *et al*. where SVRs were around 80% for both treatments (although the difference between groups was not statistically significant). This is at odds with the results of trials of non-pegylated dual therapy in previously untreated patients included in the previous assessment report[35] where only 64% of patients with genotypes 2 and 3 achieved a SVR after 48 weeks of dual therapy[56]. Nevertheless, despite the marginal difference between study groups in the Manns *et al.* trial the results of these two trials demonstrate that interferon treatment can result in SVRs in excess of 80%, albeit in one sub-group of one trial. It is likely that the 79% response to IFN and RBV in the Manns *et al.* study is by chance better than expected. Were it not by chance, there would be a case for not using PEG in genotypes 2 and 3.

Table 5 Sustained virological response rates by genotype (dual therapy)

Study	**End of follow-up response**	
	PEG IFNα + RBV	IFNα + RBV
Manns *et al.* (2002) [41]		
1	42%**	33%
2 or 3	82%	79%
4, 5, or 6	50%	38%

Fried *et al.* (2002) [49]		
1	46%*	36%
2 or 3	76%**	61%
4	77%	44%
5 or 6	--	--

* $p \leq 0.01$ for comparison between groups
** $p < 0.05$ for comparison between groups

Both trials presented SVRs according to baseline viral load[a], stratified into low or high load (≤ 2 million copies per millilitre vs. > 2 million copies per millilitre, respectively) (Table 6).

Table 6 Sustained virological response rates by baseline viral load; baseline viral load and genotype (dual therapy)

Study	**End of follow-up response**	
	PEG IFNα + RBV	IFNα + RBV
Manns *et al.* (2002) [41]		
Low viral load	78%*	56%
High viral load	42%	42%
Fried *et al.* (2002) [49]		
Low viral load	62%**	52%
Genotype 1	56%	43%
Genotypes 2/3	81%	65%
High viral load	53%***	41%
Genotype 1	41%	33%
Genotypes 2/3	74%	58%

* $p \leq 0.01$ for comparison between groups
** p=0.04 for comparison between groups
*** p=0.003 for comparison between groups

In both trials patients with low baseline viral load had higher SVRs than those with higher load, irrespective of the treatment they received. Patients in Fried *et al's* trial with a high baseline viral load were significantly more likely to have a SVR if treated with PEG than IFN (53% vs 41% respectively, p=0.003). However, in Manns *et al's* trial there was no difference in SVRs for these patients between study groups (42%, non significant p-value). Patients infected with genotype 1 in the trial by Fried *et al.* who had a high baseline viral load (i.e. those who are harder to treat successfully) were more likely to have a SVR with PEG treatment than IFN (41% vs 33% respectively). Baseline viral load data were not stratified by genotype by Manns *et al.*

Given that it was previously shown that lighter patients treated with IFN 2b have higher SVR rates than heavier patients, PEG α-2b is administered according to patients' body weight. A logistic regression analysis in the Manns *et al*. study showed that baseline weight was an

[a] We assume that baseline viral loads were determined from tests used to screen patients for inclusion. In the Fried trial the Cobas Amplicor HCV test (v. 2.0) with a lower detection limit of 100 copies/ml was used for inclusion. In the Manns trial the test used was not specified. Patients with detectable HCV RNA in serum by PCR assay were included.

important predictor of SVR. This may be due to the nature of the study design in which a fixed dose of RBV (800 mg/day) was administered together with the higher dose of PEG (1.5 μg/kg) but a variable dose of RBV (1000/1200 mg/day) was administered with the lower dose of PEG (0.5 mg/kg for 44 of the 48 weeks). Logistic regression analyses were used to further explore the relation between SVR and different doses of both PEG and RBV. The two doses of PEG were treated as categorical variables and dose of RBV was treated as a continuous variable expressed in mg/kg. The analysis found that doses of both drugs significantly predict SVR (odds ratio 1.7, p=0.002 for higher dose vs lower dose PEG, and slope 0.07, p=0.015 for RBV). The likelihood of SVR increases as the dose of RBV increases and when the dose of RBV is controlled on a mg/kg basis, the effect of a higher dose of PEG is greater compared with the lower dose. A regression model that included a term for the product of the two drug doses indicated that the optimal dose of RBV (for both safety and efficacy) was between 11-15 mg/kg (for a person weighing 75 kg this would correspond to daily doses of 800 to 1200 mg). When SVR was considered according to weight-based RBV dose, the SVR was higher in all groups when the dose of RBV was greater than 10.6 mg/kg of bodyweight (i.e. above 800mg/day).

Histological response

Of the two dual therapy trials only Manns *et al.* reported histological results. Paired biopsy samples were available in 1034 (68%) of patients randomised. Around two thirds of patients in each treatment group experienced reduced inflammation (defined as decrease of ≥ 2 units in the Knodell score for inflammation), with a reduction of -3.4 points in each case. A high proportion of patients with SVR experienced a reduction in inflammation, around 90% in each study group. For patients without SVR the proportion was in the range 38-49% with lower dose PEG treated patients experiencing the greatest reduction in inflammation. There was a reduction of fibrosis in around 20% of patients, irrespective of the treatment received. Of those patients with a SVR around 21% - 26% experienced a reduction in fibrosis, with the greatest reduction in the higher dose PEG group. Percentage reductions were marginally lower in patients without SVR, in the range 14-19%.

Compliance

McHutchison *et al.* (2002)[57] retrospectively considered the effects of adherence to therapy in one arm of each of three trials that evaluated IFN + RBV or PEG + RBV. Two of these were trials of IFN α-2b (n=1010) and one trial evaluated PEG α-2b (n=511)[41]. The analysis also included patients from the PEG α-2b monotherapy trial by Lindsay *et al.* (2001)[51] (n=607). The treatment arms selected were those in which virological response had been greatest. The data were analysed two ways. One approach assigned patients who received combination therapy into sub-groups according to their adherence. The other approach incorporated adherence as a covariate in a statistical model.

In the sub-group analysis, patients were divided according to adherence on the basis of drug dispensing/return records and patient dosing diaries. One group was 80% adherent (i.e., received ≥ 80% of their total interferon dose and ≥ 80% of the RBV dose and were treated for ≥ 80% of the expected duration of therapy). The other group underwent dose reduction (<80% of one or both drugs for ≥80% of expected duration). Patients who withdrew from the study prematurely were excluded from the analysis (These patients did have lower SVR than groups who received ≥ 80% of the assigned duration of therapy). Across the four trials 407 patients were excluded because they remained in the trial for less than 80% of the expected duration. Across the four trials 1414 patients remained in the trial for > 80% of the duration and received ≥ 80% of their medications. The primary reason for not achieving adherence to drug doses was adverse events to therapy (in > 75% of patients).

When comparing adherent and less adherent patients, they were similar in most baseline characteristics, but a larger proportion of the adherent patients were male and weighed more. Of particular interest for the current report are the findings for patients on the PEG regimens. SVR was greater for patients who were adherent to the therapy regimen than for those who received less than 80% of one or both drugs (see table 7 below).

Table 7 SVR according to adherence

Trial	**Primary intention to treat analysis**	**80% adherent patients**	**< 80% adherent patients**	**Estimated sustained response with full adherence**
Manns *et al.* (PEG + RBV)				
All patients	54%	63%*†	52%	62%
genotype 1	42%	51%*†	34%	50%
genotype 2 or 3	82%	90%	89%	
Manns *et al.* (PEG + RBV > 10.6 mg/kg)				
all patients	61%	72%	57%	71%
genotype 1	48%	63%†	34%	61%
genotype 2 or 3	88%	94%	95%	
Lindsay *et al.* (PEG monotherapy)				
all patients	23%	27%	26%	
genotype 1	14%	17%	7%	
genotype 2 or 3	49%	54%	57%	

* $p < 0.05$ for comparison between ITT analysis and 80% adherence
† $p < 0.05$ for comparison between 80% adherence and < 80% adherence

Because of the possibility of adherence being affected by selection bias, a statistical method was also used to estimate the effects of treatment adherence. These estimates are shown in Table 7 above.

These results indicate that adherence to therapy is important and enhances SVR. In particular, SVR was greater in patients receiving PEG + RBV in a fixed dose who were adherent to therapy than in the

overall analysis or in patients who were not >80% adherent. Generally, the pattern of greater SVR with adherence to therapy was only seen in patients with genotype 1 infection. In the analysed trials, the majority of patients were adherent to therapy, but this might not be the case outside the context of a trial.

Unpublished data – Hadziyannis *et al.*
(Some data from this trial have been presented at a conference but further details have been provided on a commercial in confidence basis and have been removed from this version of the report.)

The trial by Hadziyannis *et al.* (2002) published thus far only in abstract form is nonetheless considered seminal and is likely to be published soon[58]. It is described only briefly here and not considered an 'included' trial because of the lack of opportunity to fully evaluate its methods.

The trial randomly allocated 1284 previously untreated patients into four groups:

1. PEG α-2a 180 µg/wk plus RBV 800 mg/day (24 weeks) n= 207
2. PEG α-2a 180 µg/wk plus RBV 1000 – 1200 mg/day (24 weeks) n= 280
3. PEG α-2a 180 µg/wk plus RBV 800 mg/day (48 weeks) n=361
4. PEG α-2a 180 µg/wk plus RBV 1000 – 1200 mg/day (48 weeks) n=436

Because of concern that 24 weeks of treatment may not be sufficient in genotype 1, randomisation was weighted so that genotypes non-1 high and low viral loads or genotype 1 with low viral load were allocated evenly across all treatment groups. Patients with genotype 1 and high viral loads were weighted 1:1:4:4 towards the longer treatment durations. Inclusion of a non-pegylated comparison group was considered unethical given that the superiority of PEG over IFN had been already been demonstrated in large RCTs. However, it is partially relevant to this report because it appears to be the first large RCT of PEG to compare shorter with a longer treatment duration (i.e. 24 weeks vs 48 weeks).

All patients were followed-up to assess SVR 24 weeks after the end of treatment. The participants were predominantly Caucasian (85%), male (65%), genotype 1 (58%), and averaged about 5.9 million copies/ml of virus at baseline. The majority of patients with genotype non-1 were those with genotypes 2 and 3. Only a minority of genotype 4 patients were included (n=36 / 3%). A larger proportion of patients had bridging fibrosis / cirrhosis compared to previous studies of dual therapy.

(C-i-C material omitted here)

Unpublished data – Genotype 4 patients

Two trials of treatment using PEG specifically in patients with genotype 4 have been published only in abstract form. These will be briefly reviewed here because of the differential response of patients with different genotypes of infection and the dearth of information available from fully published RCTs. However, it should be noted that the methodological quality of trials cannot be fully assessed from abstracts, thus caution is advised when interpreting the results.

One trial evaluated the effectiveness of PEG α-2a[58] in 120 genotype 4 patients who were randomly assigned to PEG 180 µg/0.5ml/wk plus RBV 800 mg/day or to PEG 180 µg/wk alone. SVR data were not reported, but at end of treatment 67% of patients treated with PEG + RBV had a virological response whereas 59% of those on PEG monotherapy had a virological response. In another abstract[59], a third group from apparently the same trial was reported. These patients were randomised to receive IFN 4.5 MIU + RBV 800 mg/day. The early virological response (based on 2-log drop of HCV-RNA negatively at week 12) was 77% in the PEG + RBV group, 60% of the PEG group, and 22% in the IFN group.

A second trial[60] evaluated the effectiveness of PEG α-2b and randomised 172 patients, 80% of whom had genotype 4 infection. The patients received either PEG 100 µg/wk + RBV 800-1000mg/day based on weight, or IFN 3MU three times per week + RBV (same dose). At the time of reporting the trial was ongoing. Of those who had completed 12 weeks HCV RNA was undetectable in 71% of the PEG group and 65% of the IFN group. Of those who had completed 24 weeks of therapy, HCV RNA was undetectable in 66% of the PEG group and 59% of the IFN group.

These two trials seem somewhat inconsistent in that the first trial seemed to show much higher responses to PEG than to IFN whereas there was little difference in the second trial. This might be due to differences in efficacy between PEG α-2a and PEG α-2b in genotype 4. However, caution should be used in interpreting very preliminary results.

Summary

- In the two RCTs comparing treatment with PEG + RBV with treatment with IFN + RBV, the PEG + RBV treatment resulted in significantly higher rates of sustained response. The pooled SVR for PEG + RBV treatment was 55% (95% CI: 52%-58%) and was 46% (95% CI: 43%-49%) for IFN + RBV. The pooled relative risk was 0.83 (95% CI: 0.76-0.91).
- A published analysis of early response data from the PEG + RBV arms of these two RCTs recommended that patients with genotype 1 and early viral response (EVR) complete 48 weeks of treatment. Patients with genotype 1 without EVR at 12 weeks

should discontinue treatment and those with EVR but who are HCV RNA positive at 24 weeks should discontinue treatment. EVR does not need assessment in patients with genotypes 2 or 3 who should be treated for 24 weeks.

- Both trials found that lower age, lower body weight and non-1 genotype were associated with higher SVR. In one trial sex, lower baseline viral load and absence of bridging fibrosis/cirrhosis were also significantly associated with SVR.
- In one trial, both treatments resulted in reduced liver inflammation. Those with SVR had a greater histological response, but there were also histological responses in some patients without SVR.

3.2.3 Assessment of effectiveness in untreated patients – monotherapy (PEG)

Virological response

Table 8 shows the end of treatment and sustained virological response rates in the four RCTs which compared pegylated interferon monotherapy with non-pegylated monotherapy. The dose for non-pegylated interferon was the same in each trial (3 MIU 3 x week, except in the trial by Zeuzem *et al.* where for the first 12 weeks patients received 6 MIU 3 x week, followed by 3 MIU 3 x week for the remaining 36 weeks), however as reported in Table 2, dosages for pegylated interferon varied between different arms of the trials (see Table 8 below), consequently the table reports the response rates for the arm in which the 'standard' dose was given (e.g. 180 µg per week except Lindsay *et al* (2001) where the dose was 1.5 µg/kg per week). (See Table 9 for response rates for various doses of PEG).

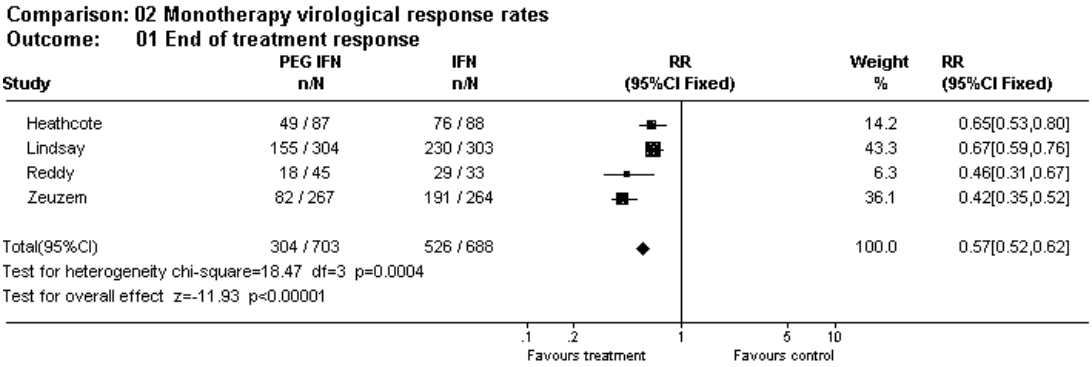
Table 8 Virological response rates for 48 weeks of monotherapy

Study	End of treatment response		End of follow-up response	
	PEG IFNα	IFNα	PEG IFNα	IFNα
Heathcote *et al.* (2000) [52]	44%	14%	30%	8%
Zeuzem *et al*. (2000) [53]	69%	28%	39%	19%
Lindsay *et al.* (2001) [51]	49%	24%	23%	12%
Reddy *et al.* (2001) [40]	60%	12%	36%	3%

All comparisons were statistically significant ($p<0.05$)

The pooled end of treatment response rates for PEG monotherapy were 57% (95% CI 53% - 60%) in comparison to 24% (95% CI 20% - 26%) for IFN monotherapy, with a pooled relative risk of 0.57 (95% CI 0.18-0.29) (Figure 3).

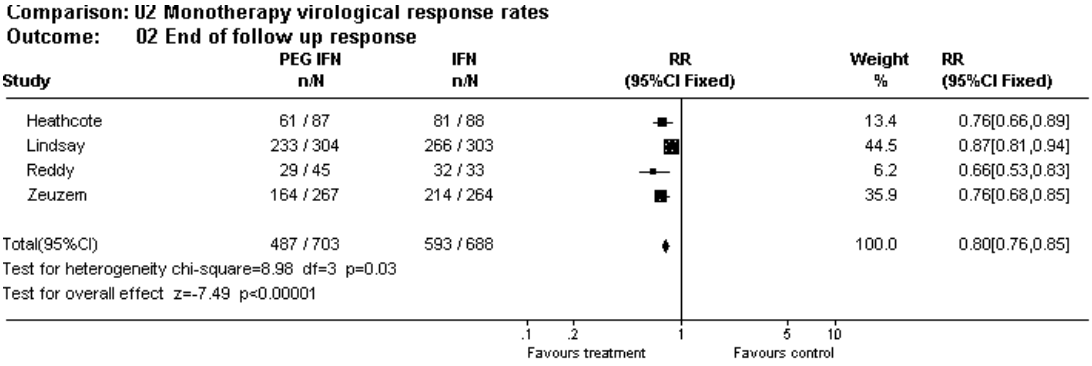
Figure 3 Pooled Relative Risk (End of monotherapy)



In all trials PEG monotherapy was significantly superior to IFN monotherapy, with SVRs in the range of 23% to 39%, and 3% to 19%, respectively.

Pooled SVRs were 31% (95% CI 27% - 34%) and 14% (95% CI 12% - 17%) for PEG and IFN monotherapy, respectively. The pooled odds ratio was 0.36 (95% CI 0.27-0.47) and the pooled relative risk was 0.80 (95% CI 0.76-0.85), respectively. In summary, monotherapy with PEG is around twice as effective in terms of sustained response than monotherapy with IFN.

Figure 4 Pooled Relative Risk (End of follow-up monotherapy)



In the studies which measured the effectiveness of different doses of pegylated interferon the response rates generally increased in line with ascending doses (Table 9). The exception was the trial by Reddy *et al.* (2001) [40] where the optimum dose appeared to be 180 µg per week rather than 270 µg. Moreover, sustained response rates were slightly higher for 1.0 µg/kg than 1.5 µg/kg in the trial by Lindsay *et al.* (2001) [51].

Table 9 Virological response rates for 48 weeks of monotherapy (dose variations – pegylated interferon only)

	PEG IFNα	**PEG IFNα**	**PEG IFNα 2a**	**PEG IFNα 2a**

	2a 45 µg	2a 90 µg	180 µg	270 µg
Reddy *et al.* (2001) [40]				
End of treatment	30%	45%	60%	56%
End of follow-up	10%	30%	36%	29%
Heathcote *et al.* (2000) [52]				
End of treatment		42%	44%	
End of follow-up		15%	30%	
	PEG IFNα 2b 0.5 µg/kg	**PEG IFNα 2b 1.0 µg/kg**	**PEG IFNα 2b 1.5 µg/kg**	
Lindsay *et al.* (2001) [51]				
End of treatment	33%	41%	49%	
End of follow-up	18%	25%	23%	

Predictors of treatment response – early response

Data were provided in the reports of the monotherapy trials on the proportion of patients who responded early who sustained their response. Reddy *et al.* reported that most patients who had a SVR had responded within the first 16 weeks of treatment. They also found that 65% of the sustained responders in the 180µg PEG group had undetectable HCV RNA by week 4. Similarly, Lindsay *et al*. reported the proportion of sustained responders who had responded at week 4. For each treatment group the likelihood of a SVR occurring was highest in patients whose first negative HCV RNA had occurred at treatment week 4, compared with those in whom HCV RNA was first negative at week 12. In the trial by Heathcote *et al.* all patients who received 180µg of PEG who had a SVR had responded by 12 weeks. In Zeuzem *et al's* trial 98% of the 103 patients in the PEG group who had a SVR had no detectable HCV RNA or the viral load decreased by a factor of 100 by week 12. In the IFN group 98% of those who had a SVR had a decrease in viral titer of at least 2 log at week 12. Hence in non-responders, treatment can be stopped at 12 weeks.

Response according to prognostic factors

Only two of the monotherapy trials (Lindsay *et al*. and Zeuzem *et al*.) performed logistic regression analysis to examine the independent effect of baseline prognostic factors on SVR (ref Zeuzem and Lindsay). Two factors shown to be significantly related to response were common to both trials: baseline viral load (≤ 2 million copies per ml) and genotype non-1. The remaining variables were all from Zeuzem *et al's* trial including: age, body surface area, baseline ALT quotient >3, no cirrhosis or bridging fibrosis, and treatment with PEG.

Table 10 shows the extent to which sustained virological response rates varied according to genotype. All of the trials, except Zeuzem *et al.* (2000), reported such information. In two trials results were aggregated to groups of genotypes (e.g. genotype 1 vs all non-1 genotypes) whilst in the other trial they were presented according to individual or smaller

aggregations (e.g. 1; 2 or 3), making it difficult to make comparisons between trials.

Table 10 Sustained virological response rates by genotype (monotherapy)

Study	**End of follow-up response**	
	PEG IFNα	IFNα
Heathcote *et al.* (2000) [52]		
1	12%	2%
1a	9%	0%
1b	20%	5%
Other than 1/unknown	51%	15%
Lindsay *et al.* (2001) [51]		
1	14%	6%
2 or 3	49%	28%
4, 5, 6	60%	0%
Reddy *et al.* (2001) [40]		
1	31%	4%
Non-1	50%	0%

Significance values for the comparison between PEG and IFN are not presented in the trials.

Patients with the harder to treat genotype 1 who received pegylated interferon did better than those who received non pegylated interferon. In one trial response rates for patients with this genotype were up to 8 times greater with pegylated interferon[40] (although the relatively fewer number of participants in this trial should be noted). Response rates for patients with sub-types 1a and 1b in the pegylated interferon group of the trial by Heathcote *et al.* (2000) [52] were also higher than for the non-pegylated group.

Table 11 reports the SVRs according to baseline viral load,[b] and stratified according to genotype. Only Heathcote *et al.* and Lindsay *et al*. provided these data. In both trials patients had higher SVRs with PEG than IFN treatment irrespective of whether they had a high or low viral load at baseline. SVRs for patients with low baseline viral load and genotype non-1 (i.e. the easier to treat patients) were in the range 55% to 68% when treated with PEG in comparison to only 10 to 36% when receiving IFN. Patients with high baseline viral load and genotype 1 (i.e. the harder to treat patients) again did better with PEG than IFN treatment but SVRs were much lower, in the range 7% to 10% and 2% to 4%, respectively.

Table 11 Sustained virological response rates by baseline viral load; baseline viral load and genotype (monotherapy)

[b] We assume that baseline viral loads were determined from tests used to screen patients for inclusion. In the Heathcote trial there was no information given about the assessment of HCV RNA levels for inclusion. In the Lindsay trial the test used was not specified. Patients with detectable HCV RNA in serum by PCR assay were included.

Study	End of follow-up response	
	PEG IFNα †‡	IFNα
Heathcote *et al.* (2000) [52]		
Low viral load	37%	5%
Genotype 1	16%	0%
Genotype non-1	55%	10%
High viral load	23%	9%
Genotype 1	10%	4%
Genotype non-1	50%	20%
Lindsay *et al.* (2001) [51]		
Low viral load	--	--
Genotype 1	34%	21%
Genotypes 2/3	68%	36%
High viral load	--	--
Genotype 1	7%	2%
Genotypes 2/3	41%	25%

† Data presented for Heathcote *et al*. is for the higher dose PEG group (180 µg)
‡ Data presented for Lindsay *et al*. is for the higher dose PEG group (1.5µg/kg)

Histological response

Paired biopsy results (i.e. from baseline to follow-up) were available in around
61%-72% of patients across the 4 monotherapy trials. Between 31%-66% of patients achieved a histological response (generally defined as a decrease of ≥ 2 units on the Knodell Histological Activity Index) across the trials, with greatest response generally amongst PEG treated patients. Histological response was highly correlated with sustained virological response in all trials, with the proportion of patients experiencing both within the range 77% to 100%, whilst among patients without SVR the proportions were much lower, in the range 4%-60% (see section 3.3.2 for results of a meta-analysis of PEG IFN 2b as dual and monotherapy on fibrosis).

The trial by Lindsay *et al.* was the only one of the monotherapy trials to report histology results separately for fibrosis and inflammation. All treatment groups experienced a decrease in hepatic inflammation, with percentage reductions in the range 47-50% (similar across treatment groups). Sustained virological responders experienced the greatest reduction in inflammation, the proportion of patients in the range 77%-90% compared to 33%-46% of those who relapsed after end of treatment response, or those who did not respond at all (33%-41%). Percentage improvements in fibrosis were in the range 20%-13% with the greatest improvement in the lower dose PEG group (0.5µg/kg) and the lowest in the IFN group. Changes in fibrosis scores followed a similar pattern to inflammation scores, with sustained virological responders experiencing a greater improvement (21%-37%) than those who relapsed or did not respond (4%-17%). Again, the proportion of patients with improvement was greatest in the higher dose PEG group and lower in the IFN group.

In Zeuzem *et al's* trial 63% of PEG treated patients experienced a histological response in comparison to only 55% in the IFN group. The

largest mean change was also experienced by PEG patients (-2.4 units in comparison to -2.0). The proportion of patients with both SVR and histological response was marginally higher in the IFN group than the PEG group (86% vs 82% respectively). For patients without a SVR the proportion experiencing histological response was much lower, with 47% in the PEG group and 44% in the IFN group.

The percentage of histological responders in the trial by Reddy *et al.* was in the range 47%-66% with the biggest and smallest improvement in the higher dose (270µg) PEG group and lower dose PEG groups (45µg) respectively. The biggest mean change in HAI score was in the 180µg PEG group, with a reduction of 2.8 units. All but two patients who achieved SVR also achieved a histological response. The proportion of patients without SVR who achieved histological response was much lower, varying between 42% and 60% in the PEG groups, and 55% in the IFN group.

In Heathcote *et al.* the proportion of patients experiencing a histological response was in the range 31% to 54% with the greatest improvement in the higher dose (180µg) PEG group. Again, SVR was highly correlated with histological response, with 80% of patients receiving IFN, 100% of patients receiving 90µg PEG and 88% of patients receiving 180µg PEG experiencing a reduction in HAI scores. For patients without SVR the proportions experiencing histological response were 26%, 33% and 35%, respectively.

Unpublished data

One trial by Pockros *et al.* (2001) is published thus far only in abstract form[61]. It is described only briefly here and not considered an 'included' trial because of the lack of opportunity to fully evaluate its methods. The trial tested PEG α-2a monotherapy against IFN monotherapy and was an open-label RCT in which 215 participants were treated with PEG α-2a 135 µg/wk, 210 participants were treated with PEG α-2a 180 µg/wk, and 214 participants were treated with IFN α-2a 3MIU 3x/wk. The participants were predominantly Caucasian (86%), male (60-70%), genotype 1 (65-70%) and averaged about 7 million copies/ml of virus at baseline. As in other trials patients were treated for 48 weeks with an untreated follow-up of 24 weeks. SVR in both PEG groups was 28% compared with 11% in the IFN group.

Summary

- In the four RCTs comparing PEG monotherapy with IFN monotherapy, the pooled SVR for PEG was 35% (95% CI: 27%-34%) and for IFN was 14% (95% CI: 12%-17%). The pooled relative risk was 0.80 (95% CI 0.76-0.85).
- Generally, the results of early viral responses in these trials indicated that the majority of patients who would have a sustained response to treatment had responded by 12 weeks of treatment.

- In the two trials that evaluated the effects of prognostic factors on SVR, lower baseline viral load and non-1 genotype were associated with higher SVR.
- When responses were considered by genotype, patients with the harder to treat genotype 1 seemed particularly to benefit from PEG treatment.
- Among patients with paired before and after treatment biopsies, histological response was highly correlated with SVR and histological responses were generally greater among patients treated with PEG.

3.2.4 Adverse events associated with pegylated interferon therapy

Dual Therapy

Trials are generally not powered to enable statistically significant differences in adverse events between study groups to be detected, making it difficult to draw firm conclusions about relative safety. However, in both trials there were a large number of possible adverse events, many of which occurred in a large proportion of patients (see table 12). For example, adverse events included effects on haematological parameters as well as flu-like symptoms, psychiatric symptoms, and gastrointestinal symptoms. However, the levels of adverse events were generally similar between regimens involving PEG and those involving IFN. The levels of treatment discontinuation and adverse events seem to be slightly higher in the trial using PEG and IFN α-2b than the trial using PEG and IFN α-2a. This could be due to the different PEG formulations, the different dosing procedure (weight-based versus fixed dose) or due to any other difference between the two trials. As there is not a within trial randomised comparison between the two PEG formulations, no conclusions about relative safety can be made.

PEG α-2a plus RBV (Fried *et al.* [49]):

Most adverse events in all groups were those commonly associated with non-pegylated IFN-based treatment. There were similar levels of discontinuations of treatment across PEG and IFN groups. There were some adverse events that were significantly less frequent in the PEG groups: depression, pyrexia, rigors and myalgia. If depression is consistently less frequent when using PEG than IFN, then this would be an important advance as the psychiatric adverse events associated with treatment are often among the most serious.

The addition of RBV to PEG α-2a did not lead to significantly more treatment discontinuations, but the RBV dose was modified in more patients than placebo.

PEG α-2b plus RBV (Manns *et al.* [41]):

As in the Fried trial, the side effect profiles for regimens involving PEG were similar to the regimen using IFN. No new or unique adverse effects were associated with the use of PEG. The levels of

discontinuation for the three regimens were virtually identical. A few adverse events were more frequent in the PEG regimens including some influenza-like symptoms in the high PEG dose. There were more injection-site reactions in the PEG groups than the IFN group, but these reactions were generally mild and not treatment limiting.

Monotherapy

As with dual therapy there were a large number of possible adverse events, many of which affected substantial numbers of patients (see table 13). For example, adverse events included effects on haematological parameters as well as flu-like, psychiatric, and gastrointestinal symptoms. Most of these were not considered serious and were not treatment limiting. There were no new or unexpected adverse events associated with PEG. The most common adverse events were flu-like symptoms that are commonly associated with IFN-based therapies. Generally the adverse events were those typical of those produced by unmodified IFN. There is some suggestion of slightly higher levels of discontinuation of treatment in the PEG groups than in the IFN groups (although this was not the case in the Zeuzem *et al*. trial[53], see table 13). There is also a slight suggestion that treatment with PEG α-2b might result in higher incidence of myalgia and injection-site inflammation than treatment with PEG α-2a.

Table 12 Adverse events (dual therapy)

	Manns *et al.* (2001)			**Fried *et al.* (2002)**					
Reported Adverse Events % of patients affected*	PEG IFN α-2b 1.5 µg/kg + RBV (800 mg) n= 511	PEG IFN α-2b 1.5 then 0.5 µg/kg + RBV (1000-1200 mg) n=514	IFN 3 MIU 3x wk + RBV (1000 – 1200 mg) n=505	PEG IFN α-2a 180 µg/wk + RBV (1000 – 1200 mg) n=453		PEG IFN α-2a 180 µg/wk + placebo n=224		IFN 3 MIU 3x wk + RBV (1000 – 1200 mg) n=444	
Discontinuation of treatment									
adverse event**	14	13	13	7.1		5.8		9.7	
laboratory abnormality				2.6		0.9		0.9	
Dose reduction†				PEG	RBV	PEG	placebo	IFN	RBV
adverse event**	42	36	34	11	21	6	17	11	22
laboratory abnormality				25	24	24	4	8	19
Due to anaemia	9	12	13	1	22	0	4	3	19
Neutropenia	18	10	8	20	1	17	0	5	<1
Thrombocytopenia				4	<1	6	<1	<1	0
Influenza-like symptoms									
Asthenia	18	16	18						
Fatigue	64	62	60	54		44		55	
Fever / Pyrexia	46	44	33	43		38		56†	
Headache	62	58	58	47		51		52	
Rigours	48	45	41	24		23		35†	
Weight decrease	29	17	20						
Dizziness	21	21	17						
Arthralgia	34	34	28	27		29		25	

Musculoskeletal pain	21	17	19			
Myalgia	56	48	50	42	42	50†
Insomnia				37	23	39
Gastrointestinal symptoms						
Anorexia	32	29	27			
Diarrhoea	22	16	17			
Nausea	43	36	33	29	26	33
Vomiting	14	14	12			
Decreased appetite				21	11	22
Psychiatric symptoms						
Concentration impairment	17	16	21			
Depression	31	29	34	22	20	30†
Insomnia	40	40	41			
Irritability	35	34	34	24	25	28
Respiratory tract symptoms						
Cough	17	15	13			
Dyspnoea	26	23	24			
Dermatological symptoms						
Alopecia	36	29	32	28	21	34
Pruritus	29	26	28	22	18	20
Rash	24	22	23			
Dry skin	24	18	23			
Dermatitis				21	13	18
Injection-site inflammation	25	27	18			
Injection-site reaction	*58*	*59*	*36*			

* events that occurred in at least 10% of patients in Manns *et al.* [41] trial

** adverse events apparently included laboratory abnormalities in the Manns *et al.* [41] trial, but adverse events and laboratory abnormalities (including neutropenia, thrombocytopenia, abnormal alanine aminotransferase levels) were reported separately in the Fried *et al.* [49] trial

‡ Some patients in the Fried *et al*. trial who required dose modifications had both adverse events and laboratory abnormalities.

† $p < 0.05$ for the comparison with PEG IFN + RBV group.

Incidence of fatigue might be slightly lower with PEG α-2b than with PEG α-2a treatment. As mentioned previously, any potential differences between PEG α-2a and PEG α-2b would need to be evaluated in the context of a randomised controlled trial with which the two formulations were directly compared.

The incidence of adverse events may be somewhat higher in the dual regimens than in monotherapy, which would imply that some adverse events are due to RBV. This would not be unexpected. However, in order to draw firm conclusions, trials in which dual therapy and monotherapy were directly compared would need to be considered. If such trials did not include a non-PEG arm they did not meet the inclusion criteria for this review as the primary question was the efficacy of PEG. (Interestingly, the Fried *et al*. trial[49] did include a comparison between PEG α-2a plus RBV and PEG α-2a plus placebo. These two arms did not appear to differ consistently in adverse events.) A previous review[35] did compare IFN plus placebo with IFN plus RBV and reported findings that haematological events such as anaemia were greater when RBV was part of the regimen.

PEG α-2a:
In the three trials using PEG α-2a there were few differences in adverse effects between PEG and IFN groups. In the Heathcote *et al*. trial[52] there were more instances of myalgia and inflammation of the injection site in the high dose PEG group than in low dose PEG or IFN groups. In the Reddy *et al*. trial[40] depression, pruritus and irritability were more common in the PEG groups than the IFN group. (Recall that depression was less frequent in the PEG group in the Fried dual therapy trial. Therefore, conclusions about depression should be tentative at best.) Dizziness and myalgia were higher in the IFN group than in the PEG groups. This trial reported more dose modifications in the groups receiving 270 µg PEG than in the other groups and more discontinuations in the PEG groups than in the IFN group. Differences between arms in this trial in particular should be viewed with caution as the numbers of patients in the groups in this trial were relatively small and could result in spurious differences. In the Zeuzem *et al*. trial it appears there were slightly fewer adverse events in the PEG group than the IFN group. In general, however, all differences in self-reported adverse events should be viewed with caution in open label trials.

In the Heathcote *et al*. trial there were significantly fewer patients with low platelet counts (< 50,000/mm^3) in the IFN group than in the two PEG groups. Zeuzem *et al*. reported than thrombocytopenia was rare in both groups and Reddy *et al.* reported dose-dependent drops in platelets in the PEG groups that corrected by week 52. There is little additional indication of dose-related increases in adverse events, although this possibility is not strongly tested in the included studies.

PEG α-2b:
Only one trial[51]compared PEG α-2b with IFN α-2b. In this trial PEG was considered to be comparable to IFN in safety and tolerability with no new or
unexpected adverse events specific to PEG. The higher doses of PEG did produce somewhat higher frequency of fever and chills. Injection-site reactions were approximately twice as frequent in the PEG groups, but were generally mild and not treatment limiting. Dose reductions for thromobocytopenia were more common in the PEG groups and dose reduction for neutropenia was more frequent in the 1.5 µg/kg PEG group. Dose reductions increased with higher doses of PEG, but treatment discontinuations were comparable across the PEG groups and slightly higher than in the IFN group.

Summary
In summary, regimens involving PEG appear to be fairly well tolerated and do not differ substantially in levels of adverse events from regimens involving unmodified IFN. Dose modifications may be needed in more patients with higher doses of PEG (particularly monotherapy). There is

some suggestion that dual therapy including RBV may result in more adverse events than PEG monotherapy.

Table 13 Adverse events (monotherapy)

	Heathcote, *et al*, (2000) [52]			**Zeuzem, *et al*, (2000) [53]**		**Lindsay, *et al*, (2001) [51]**				**Reddy, *et al*, (2001) [40]**				
Reported Adverse Events % of patients affected*	PEG IFN α-2a 90 µg/wk n=96	PEG IFN α-2a 180 µg/wk n=86	IFN α-2a 3 MIU 3x/wk n=86	PEG IFN α-2a 180 µg/wk n=265	IFN α-2a 6 MIU then 3 MIU‡ n=261	PEG IFN α-2b 0.5 µg/kg/wk n=315	PEG IFN α-2b 1.0 µg/kg/wk n=297	PEG IFN α-2b 1.5 µg/kg/wk n=304	IFN α-2b 3 MIU 3x/wk n=303	PEG IFN α-2a 45 µg/wk n=20	PEG IFN α-2a 90 µg/wk n=20	PEG IFN α-2a 180 µg/wk n=45	PEG IFN α-2a 270 µg/wk n=40	IFN α-2a 3 MIU 3x/wk n=30
Discontinuation of treatment														
adverse event	7	13	8	7	10	9	11	9	6	10	0	22	20	9
laboratory abnormality	4	1	2											
*Dose reduction***														
adverse event	2	14	14	8	11	9	14	19	6				49	
laboratory abnormality†				14	9									
Neutropenia	9	10	14											
Thrombocytopenia	18	18	6											
Influenza-like symptoms														
Fatigue	53	62	60	60	65	43	51	45	50	70	85	67	70	70
Fever / Pyrexia	29	38	36	37	52	31	45	44	30	15	10	24	28	30
Headache	54	50	53	60	66	61	64	64	58	40	35	58	48	60
Rigours / Chills	38	43	45	27	43	34	40	44	33	5	20	47	50	47
Dizziness	20	15	16	23	16					10	20	13	18	23
Arthralgia										20	40	18	30	23
Musculoskeletal pain						19	28	20	22					
Myalgia	36	51	38	42	43	48	54	61	53	40	65	31	48	63

Gastrointestinal symptoms														
Anorexia / Decreased appetite	15	14	7	20	21	10	20	25	17	15	20	16	13	7
Diarrhoea	21	24	19	19	20					25	25	31	33	20
Nausea	30	34	34	21	35	21	26	25	20	45	15	44	30	47
Vomiting	12	13	15	6	12					20	0	16	3	17
Upper abdominal pain	19	26	24	13	14					30	10	18	28	17
Psychiatric symptoms														
Concentration impairment	6	7	12	5	11					10	20	7	30	7
Depression	21	26	21	16	23					30	35	27	38	10
Insomnia	19	19	22	18	24	17	23	20	23	25	5	33	30	23
Irritability						19	18	17	24	35	20	29	33	13
Anxiety	11	3	7											
Respiratory tract symptoms														
Cough	10	17	5	9	10									
Sinusitis	12	8	7											
Nasopharyngitis				11	8									
Dermatological symptoms														
Alopecia	15	17	22	27	37	20	22	34	22	5	30	22	25	20
Pruritus	16	16	8	18	12					10	15	11	13	3
Dermatitis	8	17	7							15	0	13	28	7
Injection-site inflammation	15	31	14	10	7	44	42	40	16	35	30	24	25	20
Other														
Pain	10	10	12							20	0	20	13	13
Pain in limb	11	8	5							15	25	9	8	13
Back pain											15	16	15	17

Epistaxis	11	7	14												

* adverse events during treatment or first 8 weeks of follow-up occurring in at least 10 percent of patients in Heathcote, *et al*[52] Adverse events reported in Reddy[40] were those observed in at least 10% of patients. Discontinuation in the Zeuzem[53] , Lindsay[51], and Reddy[40] trials was not reported separately for adverse event and laboratory abnormalities. Therefore the value reported for adverse events reflects the total proportion of treatment discontinuations. Some patients in the Zeuzem trial had more than one adverse event.

[†]Regimen was IFN α-2a at 6 MIU 3x/wk for 12 weeks than 3 MIU 3x/wk for 36 weeks.

** Dose reductions in the Lindsay trial[51] were not reported separately for adverse events and laboratory abnormalities. Dose reductions in the Reddy trial[40] were not reported for all treatment arms and were not reported separately for adverse events and laboratory abnormalities in the reported arm.

† Laboratory abnormalities that could result in dose modifications in the Zeuzem trial[53] consisted of neutropenia, thrombocytopenia, abnormal alanine aminotransferase values, hypothyroidism, and hyperthyroidism. Some patients in this trial who required dose modifications had both an adverse event and a laboratory abnormality

All of the tested treatment regimens have effects on levels of haemoglobin, platelets and neutrophils. Generally, discontinuations due to anaemia, thrombocytopenia or neutropenia were rare. Most trials reported patterns of decreased haemoglobin, platelets and neutrophils associated with treatment, which generally stabilised during treatment and returned to baseline levels after the end of treatment. These effects require careful monitoring during treatment, in case dose modification or discontinuation should become necessary. The effects on haematological parameters may be somewhat greater in PEG regimens than in IFN regimens.

Two trials reported deaths after the end of treatment[49;52]. In the Fried *et al*. trial none of the three deaths was considered treatment related. In the Heathcote *et al*. trial, any potential relationship between treatment and the four deaths was unclear. Two patients died of hepatic failure, 420 and 179 days after the end of treatment, one patient died of hepatic neoplasm 219 days after the end of treatment and one patient (180 µg PEG) died of a cerebral haemorrhage after a suspected methadone overdose, 24 days after the end of treatment.

3.3 Evidence from related systematic reviews

Two systematic reviews identified during literature searching also shed light on the clinical-effectiveness of pegylated interferon. A third review is planned by the Cochrane Hepato-Biliary Group.

3.3.1 Agency for Healthcare Research and Quality (AHRQ)

The Agency for Healthcare Research and Quality (AHRQ) recently published a report for the U.S. Department of Health and Human Services on Management of Chronic Hepatitis C[62]. This report was also summarised in a journal publication by Chander *et al.* (2002) [63].

Methods such as searching and implementation of inclusion / exclusion criteria, were very similar to those of the current review. The method of quality assessment of included studies was somewhat different; using a scale to rate studies as opposed to assessment of the individual components of study methodology. Narrative approaches to synthesis were followed, as opposed to a mixture of narrative and quantitative approaches used in the current report.

A broader range of questions was posed:

1. "How well do the results of initial liver biopsy predict measures of disease progression and outcomes of treatment in patients with chronic hepatitis C, taking into consideration patient characteristics such as viral genotype?
2. How well do biochemical blood tests and serological measures of fibrosis predict the findings of liver biopsy in patients with chronic hepatitis C?
3. What is the efficacy and safety of current treatment options for chronic hepatitis C in treatment-naïve patients, including pegylated

interferon plus ribavirin, pegylated interferon alone, interferon plus ribavirin, and interferon plus amantadine?

4. What is the efficacy and safety of current interferon-based treatment options (including interferon alone) for chronic hepatitis C in selected sub-groups of patients, especially those defined by the following characteristics: age less than or equal to 18 years, race/ethnicity, HCV genotype, presence or absence of cirrhosis, minimal versus decompensated liver disease, concurrent hepatitis B or HIV infection, non-response to initial interferon-based therapy, and relapse after initial interferon-based therapy?
5. What are the long-term clinical outcomes (greater than or equal to 5 years) of current treatment options for chronic hepatitis C?
6. What is the efficacy of using screening tests for hepatocellular carcinoma to improve clinical outcomes in patients with chronic hepatitis C?
7. What are the sensitivity, specificity, and predictive values of tests that could be used to screen for hepatocellular carcinoma (especially respectable carcinoma) in patients with chronic hepatitis C?" (p. 6)

The most directly relevant question to the current review is question 3 (although question 2 is considered in section 3.7. With regard to the efficacy of PEG, the AHRQ review did not report on any trial data that is not included in the current review and concluded that "studies of treatment-naïve patients with chronic hepatitis C showed greater efficacy of pegylated interferon plus ribavirin when compared to standard interferon plus ribavirin or peginterferon alone, greater efficacy of peginterferon when compared to standard interferon, and no significant increase in efficacy with standard interferon plus amantadine when compared to interferon monotherapy; for non-responders and relapsers, standard interferon plus ribavirin was more efficacious than interferon alone; little evidence existed on treatment efficacy in HIV-infected patients, renal patients, haemophiliacs, or injecting drug users." (p.4)

Additional results from the AHRQ report were:

1. "studies were relatively consistent in suggesting that advanced fibrosis or cirrhosis on initial liver biopsy may independently predict a slightly decreased likelihood of SVR to treatment…
2. studies were mildly consistent in suggesting that interferon-based therapies decrease the risk of HCC and cirrhosis in complete responders…
3. one study suggested that HCC was detected earlier and was more often resectable in patients who had quarterly screening with serum alpha-fetoprotein (AFP) and ultrasound than in those who had usual care…
4. studies were relatively consistent in suggesting that a serum AFP greater than 10 ng/ml has a sensitivity of 75 to 80 percent and a specificity of about 95 percent in screening for HCC, and a serum AFP greater than 400 ng/mL has a specificity of nearly 100 percent for detection of HCC." (p4)

3.3.2 Poynard *et al.*

Poynard *et al.* [64] conducted a meta-analysis to estimate the impact of pegylated interferon 2b on liver fibrosis. Data from four trials that tested either IFN α-2b or PEG IFN α-2b regimens in chronic hepatitis C were combined. These regimens could be either monotherapies or could include dual therapy combining RBV with IFN or PEG (The two trials that used PEG dual therapy were included in the current review[41;51]). The 'control' regimen was considered to be IFN α-2b at a dose of 3MIU 3 times/week for 24 weeks. The results from the 10 included regimens were considered primarily for changes in liver fibrosis.

Data from 3010 treatment naïve patients with pre- and post-treatment biopsies were pooled. The inclusion and exclusion criteria were generally the same as those outlined for the trials included in the current review – patients with chronic hepatitis C, but without significant co-morbidities. The particular treatment regimens included are listed in appendix 7. Liver biopsies were scored using the METAVIR scoring system (one grade in METAVIR is equivalent to 4 grades in the Knodell index, which is twice the usual definition of histological improvement). Fibrosis was scored on a scale of 0 to 4. Activity (i.e. necroinflammatory activity) was also scored on a scale of 0 to 3. Different treatment regimens were compared for the percentage of patients who improved by at least one fibrosis stage, remained stable, or worsened by at least one stage. Regimens were also compared according to the fibrosis progression rates per year before and after treatment. The impact of different regimens on the percentage of patients with significant fibrosis at the second biopsy was also assessed adjusted by other risk factors in multi-variate analyses. Finally, the hypothesis that the 'non-control' regimens could reverse cirrhosis was tested.

A range of detailed results were presented. The primary results in terms of liver fibrosis were:

1) necrosis and inflammation improvement ranged from 39% to 73% (PEG 1.5 µg/kg + RBV);
2) fibrosis worsening ranged from 23% to 8% (PEG 1.5 µg/kg + RBV);
3) all regimens significantly reduced fibrosis progression rates relatively to pre-treatment;
4) reversal of cirrhosis (change in fibrosis score from pre-treatment) was observed in 49% of patients who had baseline cirrhosis;
5) six factors were independently associated with the absence of significant fibrosis after treatment: baseline fibrosis stage, SVR, age < 40 years, body mass index < 27 kg/m^2, no or mild baseline necroinflammatory activity (based primarily on necrosis), and viral load < 3.5 million copies/ml.

There was significantly less worsening of fibrosis among patients who achieved SVR (7%) than among relapsers (17%) or non-responders (21%).

There was also significantly more necroinflammatory activity improvement in those with SVR than in relapsers or non-responders. Rates of fibrosis progression were lower after treatment in both virological responders and non-responders with no significant differences between different treatment regimens (but there was a significant difference between responders and non-responders). Histological response was related both to viral response and several baseline factors. The results suggest that even without a SVR treatment may slow the progression of liver fibrosis and would therefore argue against early cessation of treatment in patients without a virological response. Histological response should also be evaluated in these patients. The question of which regimen would be best for such patients should be evaluated prospectively.

Some caution should be used in interpreting this report because only some of the comparisons are randomised, within-trial comparisons. In addition, most of the included regimens (particularly those using PEG) were tested in only one or two trials. Finally, this analysis only considered trials using PEG or IFN α-2b thus the findings cannot necessarily be generalised to PEG or IFN α-2a.

3.3.3 Cochrane Hepato-Biliary Group

'Pegylated interferon alpha for chronic hepatitis C'[65] is the title of a protocol for a systematic review currently on the Cochrane Library. The review will assess the clinical-effectiveness of RCTs of pegylated interferon in previously untreated patients, relapsers and non-responders to previous treatment. The review will assess the effectiveness of monotherapy (PEG vs no intervention; PEG vs placebo; PEG vs IFN) and dual therapy (PEG + RBV vs IFN + RBV). Primary outcomes will include SVR, liver related morbidity, and survival, whilst secondary outcomes include end of treatment virological response; end of treatment and sustained biochemical response; histological response, adverse events, treatment discontinuation, dose reduction, quality of life and cost-effectiveness. Sub-group analyses will be performed to assess the effect of factors including gender, genotype, baseline viral load, presence of bridging fibrosis and cirrhosis on SVR. Analyses will also examine the effect of PEG dose (< than versus 180 µg/week, < versus 1.5 kg/week or more), duration of therapy (<24 weeks vs > 24 weeks), and formulation of PEG on SVR (2a vs 2b).

3.4 Treatment for patients with co-morbidities

The question of treatment of hepatitis C in patients who have other illnesses such as HIV or haemophilia is important, but has received relatively little attention. The major trials testing the efficacy of PEG and other hepatitis C treatments have excluded patients with significant co-morbidities.

The recent systematic review by the AHRQ (discussed above in section 3.3) specifically addressed the question of treatment of hepatitis C with co-morbidities[62]. This review reported on three trials that tested treatment in patients undergoing haemodialysis, in patients with haemophilia, or in patients co-infected with hepatitis C and hepatitis B. However, none of these trials tested the efficacy of PEG in these groups. Likewise, the search performed in the current review revealed no full reports of controlled trials of PEG in patients with co-morbidities. However, many patients with HCV do have other co-morbidities and some evidence, albeit not using PEG, is available.

Many patients with HIV also are infected with hepatitis C and therefore the question of efficacy of HCV treatment in patients co-infected with HIV is germane. HIV and HCV share common routes of transmission. With recent improvements in the treatment of HIV leading to increased life expectancy, the treatment of co-infections such as hepatitis C in this population has received more attention. Between 7% and 57% of patients with HIV are also infected with hepatitis C[66]. The variation in co-infection rates is related to the varying hepatitis C risk factor distributions of the study populations. Among co-infected patients, hepatitis C is the leading non-acquired immunodeficiency syndrome cause of death, and end stage liver disease due to hepatitis C accounts for up to 50% of deaths[66]. Although the mechanisms are not fully understood, it appears that HIV is associated with accelerated liver disease and reduced survival in hepatitis C infected patients. Likewise, hepatitis C is an independent factor associated with HIV progression to AIDS and AIDS-related death[66]. Treating co-infected patients is complicated by the possibility of adverse drug interactions.

A recent systematic review of the management of co-infection with HIV and HCV[66] revealed no placebo controlled trials of HCV treatment conducted in co-infected patients. Twelve studies using either IFN monotherapy or IFN + RBV showed equivalent SVR in co-infected and HCV infected patients. However, none of these studies used PEG and none were RCTs.

There are on-going trials of treatment in patients with co-infections (see Appendix 11). Preliminary reports from some trials are available in abstract form. Only three trials that included a comparison between PEG and non-pegylated interferon are mentioned here. It should be noted that the methodological quality of studies reported only in abstracts cannot currently be fully evaluated.

- Two abstracts[67;68] report preliminary data from a trial that involved 416 patients co-infected with HIV. Patients were randomised to receive either PEG α-2b (1.5 mg/kg/wk) + RBV (800 mg/day) or IFN α-2b (3 MIU 3x/wk) + RBV (800 mg/day) for 48 weeks. Although a 24 week follow-up for the trial was scheduled the abstract only reported results from the end of treatment[67]. An end-of-treatment virological response was seen in 44% of the PEG group and 27% of the IFN group ($p = 0.009$). The response rate for

patients with genotypes 1 or 4 was 19% whereas the response rate for patients with genotypes 2 or 3 was 57%. (The abstract did not specify whether these response rates by genotype were in the IFN or the PEG group.) Treatment was discontinued in 30% of patients and severe adverse events occurred in 24% (42 in the IFN group and 57 in the PEG group, $p = 0.08$). The second abstract[68] considered the effects of HCV treatment on HIV viraemia concluding that the treatment did not significantly increase or decrease plasma HIV viraemia during the first six months of treatment. At week 48, a mean decrease of 115/mm^3 CD4 cells was observed. The results did not support a benefit of PEG in treating HIV infection in HCV co-infected patients.

- Another study[69] included 47 IDUs who were co-infected with HIV and HCV. The patients were treated with IFN α-2b (5MIU daily for 3 mo then 5 MIU 3x/wk) + RBV (1000-1200 mg/day) or PEG α-2b (1.5 mcg/kg/wk) + RBV (800 mg/day). Treatment was for 24 weeks for genotypes 2 and 3 and for 48 weeks for genotypes 1 and 4. It is not clear when results were obtained. Among those receiving IFN + RBV, 23% had sustained response, 21% early response, 29% were non-responders, and 27% discontinued therapy. Among those receiving PEG + RBV, 20% had sustained response, 36% early response, 12% were non-responders, and 32% discontinued therapy. These results indicate lower rates of sustained response than in patients who are not co-infected. This may be due to high levels of discontinuation due to side effects such as psychiatric co-morbidity and drug interactions with concomitant highly active anti-retroviral therapy (HAART).
- Another abstract[70] offered a preliminary report of 36 patients randomised to receive IFN 2b (Intron A 3MIU 3x/wk) + RBV (800 mg/day) or PEG 2b (Peg-Intron 1.5 µg/kg/wk) + RBV (800 mg/day) for 6-12 months according to genotype. No viral response data were presented, but the PEG treatment was associated with significantly greater neutropenia than IFN. Even low dose RBV may lead to life-threatening lactic acidosis in patients taking nucleoside reverse transcriptase inhibitors-containing HAART. These findings suggest that co-infected patients should be very carefully monitored during HCV treatment.
- No trials were located in which patients with other co-morbidities were treated in a design involving a control condition.

3.5 – Results – Re-treatment of non-responders to interferon monotherapy

This section is split into two sub-sections, the first looking at the evidence for the effectiveness of re-treatment with PEG dual therapy, and the second looking at re-treatment with non-PEG dual therapy.

3.5.1 Assessment of effectiveness of re-treatment - dual therapy (PEG + RBV)

No fully published trials of re-treatment of non-responders to IFN monotherapy with PEG were identified in this review. The paucity of literature is most likely because of the relatively recent introduction of pegylated interferon. However, conference abstracts were located relating to 2 ongoing studies. As these have yet to undergo peer review their results should be interpreted with caution. Furthermore, neither of these studies include an arm in which patients receive IFN monotherapy as a comparator. This is likely because advances in therapy over recent years would probably make it now unethical to re-treat patients with IFN monotherapy. Therefore, we can only make indirect comparisons between re-treatment with PEG dual therapy and IFN monotherapy.

Shiffman (2002) [71] presents the results to date of the lead-in phase of the HALT-C trial (Hepatitis C Anti-viral Long Term Treatment against Cirrhosis) in which patients with advanced fibrosis or cirrhosis who remain HCV positive despite dual therapy with PEG receive long term maintenance PEG interferon monotherapy over 4 years in an attempt to prevent histological progression, reduce the development of hepatocellular carcinoma and lessen the need for hepatic transplantation. The trial is supported by US National Institute of Diabetes and Digestive and Kidney Diseases, and Hoffman-LaRoche (USA). Non-responders to IFN monotherapy and dual therapy with IFN+RBV were re-treated with PEG 2a (180mg/wk) + RBV (1,000 mg/day) for 24 weeks. Patients HCV RNA positive at week 20 were classed as non-responders and entered the long term HALT-C trial, whilst those who were RNA negative were treated until week 48, and then followed up until week 72. Results are currently presented for 212 of the 863 patients enrolled in the trial for whom SVRs are available. The majority of patients had advanced fibrosis or cirrhosis and were infected with genotype 1 and were predominantly male. End of treatment responses were achieved in 53%, with SVR achieved in only 20%. SVRs were significantly greater in patients who had previously failed IFN monotherapy than those who had failed dual therapy with IFN + RBV (34% vs 11%, $p<0.005$). Patients with genotype non-1 and who were less than 50 years of age also achieved higher SVRs. Factors not related to SVR included gender, body weight or baseline viral load. Again, caution must be exercised in interpreting these results given its status as a conference abstract, and the absence of any control/comparison group.

Jacobson *et al.* (2002) [72] present the results to date of a Schering-Plough supported RCT in which patients who had failed to respond either to IFN monotherapy, or IFN dual therapy, or who had relapsed following IFN dual therapy were randomised to receive a lower dose of PEG 2b (1.0µg/kg) with a higher dose of RBV (1000-1200mg per day), or conversely a higher dose of PEG (1.5µg/kg) and lower dose of RBV (800mg per day). Treatment is planned for 48 weeks with cessation after 24 weeks if HCV RNA remains positive. Results are presented for the 231 of the 330 patients enrolled who have completed 24 weeks of treatment. Response rates at 24 weeks of treatment were highest for relapsers to previous IFN + RBV therapy followed by non-responders to IFN

monotherapy and were lowest in non-responders to dual therapy with IFN+RBV, irrespective of the dose of PEG.

As might be expected, both of these studies suggest that re-treatment with PEG dual therapy is more effective for patients who have failed IFN monotherapy than those who failed previous dual therapy with IFN+RBV. Shiffman (2002) [73] suggests that the likelihood that re-treatment will be effective is directly related to the differences in efficacy between the initial and the re-treatment regimens. The expected range for SVR during re-treatment can be estimated by calculating the difference in end of treatment virological response rates between the two therapies and the relapse rate of the newer treatment. It is estimated that non-responders to IFN monotherapy would have a higher chance of an end of treatment response when re-treated with PEG dual therapy than dual therapy with IFN.

In summary, the evidence for the clinical-effectiveness of re-treatment with PEG dual therapy is currently only available in conference abstract form and is based on two studies, one of which is an uncontrolled evaluation of dual therapy as a lead in phase to an RCT of long term maintenance therapy, and the other an RCT comparing two different dose regimens of dual PEG. Preliminary evidence suggests higher EOTR and SVRs for patients re-treated after failing IFN monotherapy than those re-treated after failing IFN + RBV dual therapy. Further RCTs are required, comparing PEG dual therapy with IFN dual therapy.

3.5.2 Assessment of effectiveness of re-treatment - dual therapy (IFN + RBV)

Given the lack of fully published evidence for the clinical-effectiveness of re-treatment of patients with pegylated interferon we turned to examine the evidence base for re-treatment with non-pegylated interferon. To be included in this section of the review studies had to randomly assign patients who had failed a previous course of monotherapy (IFN) to dual therapy (IFN+RBV) or to monotherapy (IFN). Trials with more than one comparator were also eligible as long as there was an arm that received IFN monotherapy (e.g. IFN+RBV vs IFN +/- placebo vs IFN + amantadine). Trials that included a mixture of non-responders and relapsers to previous interferon monotherapy were also eligible. The minimum period of previous treatment had to be three months.

The clinical-effectiveness of re-treatment with non-pegylated dual therapy is presented below firstly in terms of the results of previous systematic reviews identified, secondly the results of a meta-analysis of individual patient data, and thirdly through the results of our own meta-analysis of all published studies identified to date.

Results of previous systematic reviews of re-treatment
Our previous assessment report included 12 trials assessing the effectiveness of dual therapy (IFN+RBV) as re-treatment for patients who

either failed to respond, or relapsed following a previous course of interferon monotherapy. Since publication of the report in late 2000 a number of systematic reviews have emerged that have also addressed the question of re-treatment of interferon monotherapy non-responders[62;63;74-77]. These reviews included some of the 12 trials in the assessment report, in addition to a number other relevant trials, most of which were published since our original assessment report. Rather than performing data extraction and critical appraisal of these additional trials (and thus duplicating the effort of others) we used the systematic reviews themselves as a basis for estimating the clinical-effectiveness of re-treatment. We critically appraised the reviews, and were satisfied that they had systematically searched for relevant trials, assessed their quality, and synthesised their results appropriately (see Table 14).

Table 14 Quality Assessment of Included Systematic Reviews

Review	Good relation between study question and inclusion/ exclusion criteria	Evidence of thorough search for all relevant research	Validity of included studies adequately assessed	Sufficient detail of individual studies presented	Primary studies summarised appropriately
Cheng, *et al 2001* [74]	✓	primarily Medline	✓	✓	✓
Cummings *et al* (2001) [75]	✓	✓	✓	✓	✓
Kjaergard, *et al* (2002) [78]	✓	✓	randomisation and blinding	in ancillary table	✓
AHRQ (2002) [62;63]	✓	✓	✓	✓	narrative only
San Miguel, *et al*, (2002) [77]	✓	✓	✓	✓	✓

The inclusion criteria used in these reviews were broadly similar to those used in the current review. Each of these reviews included only RCTs in their primary analyses. Two reviews (Cheng *et al.* and San Miguel *et al.*) used more stringent inclusion criteria with regard to doses of IFN and RBV, dose frequency and treatment duration. The other three reviews did not restrict inclusion based on these criteria. In general, trials have tended to be very similar in these characteristics such that the use of these inclusion criteria is not likely to have had much effect on study selection. Three reviews (Cheng *et al.*, Kjaergard *et al.*, and San Miguel *et al.*) explicitly excluded studies in patients with other diseases such as HIV infection or haemophilia. One review (Kjaergard *et al.)* included trials published as conference abstracts. Sustained virological response in all reviews was based on results from ≥ 24 weeks after the ending of treatment.

All reviews assessed the quality of included studies. The Cheng *et al.* and Kjaergard *et al.* reviews reported for each included study whether there was an appropriate generation of the allocation sequence, appropriate allocation concealment, and whether the trial was double blind. This

approach is very similar to that used in the current review. The remaining three reviews assessed study quality using scales with each using a different scale. The total quality scale scores were presented in the Cummings *et al.* and San Miguel *et al.* reviews whereas quality sub-scale scores (including a bias subscale) as well as a total quality score was presented in the AHRQ review.

Table 15 presents a summary of results from the 4 reviews that performed statistical meta-analyses pertaining specifically to the comparison of IFN + RBV versus IFN re-treatment in previous non-responders to IFN monotherapy.

Table 15 Results from previous systematic reviews of IFN + RBV v IFN in non-responders to previous IFN monotherapy

Study	**Number of included studies and total n**	**Pooled SVR result**
Cheng, *et al.* (2001) [74]	8 trials n = 726	▪ SVR IFN + RBV = 13.2% (95%CI, 10.0%-17.3%) ▪ OR: 4.9 (95% CI, 2.1-11.2) in favour of IFN + RBV
Cummings *et al.* (2001) [75]	11 studies n = 899	▪ SVR IFN + RBV = 14% (95% CI, 11-17%) ▪ SVR IFN = 2% (95% CI, 1%-4%) ▪ Risk Difference = 7.0% (95% CI, 2%-13%)
Kjaergard *et al.* (2002) [78]	10 trials	▪ Relative risk of not having SVR: 0.89 (95% CI, 0.83 to 0.96) in favour of IFN + RBV
San Miguel, *et al*. (2002) [77]	5 trials n= 786	▪ SVR IFN + RBV = 12.6% (95% CI, 9.5%-16.3%) ▪ SVR IFN = 2% (95% CI, 0.9 ▪ %-4.0%) ▪ OR: 5.49 (95% CI, 1.9-15.89)

NB. The AHRQ review did not perform quantitative synthesis
OR = Odds Ratio

In terms of results there was general concordance between the reviews with pooled SVRs for re-treatment with dual therapy in the range 12%-14% compared to 2% for re-treatment with monotherapy only, indicating that dual therapy is far more effective as a re-treatment strategy. However, given the response rates of 49% for patients re-treated with IFN + RBV following relapse from previous monotherapy[33] these results do appear disappointing.

Only one review considered the effects of prognostic variables on response by meta-regression[78]. The Kjaergard *et al.* review found a significant positive association between the effect of IFN + RBV and the proportion of patients with genotype 1 after adjusting for previous treatment, intervention regimen and patient characteristics, suggesting the patients with genotype 1 benefit more from IFN + RBV as opposed to IFN alone than do patients with other genotypes. There was a significant negative association between the benefit of dual therapy and the proportion of

patients with cirrhosis, suggesting that patients with cirrhosis benefit less from combination therapy. The Cummings *et al.* review considered only the effects of treatment variables in meta-regressions.

Two reviews considered effects of prognostic variables by means of sensitivity analyses[74;77]. In the Cheng *et al.* review SVRs were determined after excluding studies containing the highest or lowest proportion of patients with the covariate. The overall SVR for trials that included more than 50% of patients with genotype 1 was decreased compared with the primary analysis. Minimal differences from the primary analysis were detected when sensitivity analyses were performed on trials varying in baseline levels of HCV RNA. The San Miguel *et al.* review considered trials with more than or less than 50% of patients with genotypes 1 and 4. The confidence intervals for these analyses overlapped, but a greater response was seen in trials with a lower proportion of patients with genotypes 1 and 4.

Results from an individual patient data meta-analysis

Cammà *et al.* (2002) [45] questioned the usefulness of re-treating all patients indiscriminately given the disappointing results from the systematic reviews discussed above. To that end they performed an independent patient data meta-analysis to re-assess efficacy and safety of re-treatment with IFN and RBV; to assess the best re-treatment schedule; and to identify predictors of sustained response to enable better targeting of therapy to patients most likely to respond. Data on 581 non-responders to previous IFN monotherapy were obtained from 10 European (mostly Italian) treatment centres, published as RCTs (n=3), CCTs (n=1), and prospective cohort studies (n=6). Five of the studies had been fully published, three were conference abstracts and two remained unpublished, representing 312 (54%), 189 (32%) and 80 (14%) of the patients, respectively. The sample comprised mostly males (66%), mean age 46 years, and infected with genotype 1 (54%), with only 11% having cirrhosis. Re-treatment regimens varied from 3 MIU IFN 3 x week + RBV over 6 months to 12 MIU 3 x week + RBV over 12 months. Around two-thirds of patients were re-treated for a total of 12 months (61.3%). The type of IFN used included 2b (91%), Leucocytic N-3 (5.7%), but 2a does not appear to have been used.

A 'complete' sustained response (SR; defined as both a biochemical and a virological response) was achieved by 15.7% (95% CI 15.6%-22%) of patients (n=88/559), whilst 9.2% of patients (n=54/581) withdrew due to side effects associated with re-treatment. There was no statistically significant difference in the probability of achieving a complete SR according to prognostic factors such as genotype, baseline liver histology, and baseline viral load. Uni-variate analysis identified three factors significantly associated with a complete SR:

- younger age;
- γ-glutamyltransferase levels;
- re-treatment with a total IFN dose of ≥ 432 MIU.

Marginally significant was absence of cirrhosis (p=0.061). A sub-group analysis was performed on the 396 patients re-treated with the higher total dose of IFN (≥ 432 MIU) to assess whether there was a significant effect of duration of treatment. A complete SR was achieved in 74 (18.6%; 95% CI 14.9-22.6%) of these patients. Among these patients the likelihood of a complete SR was significantly lower when the higher dose was administered over a shorter period (≤ 26 weeks) (n=7/73; 9.5%; 95% CI 3.5%-19.5%) versus a longer period (>26 weeks) (n=67/323; 20.7%; 95% CI 16.4%-25.3%) (p=0.027).

Multi-variate analysis identified the following factors as independent predictors of complete SR (in decreasing order of significance):

- re-treatment with a total IFN dose of ≥ 432 MIU (OR 2.25);
- normal pre-treatment γ-glutamyltransferase levels (OR 0.54);
- age (<45 years old) (OR 0.62).

These factors were grouped together in combinations to be applied to sub-groups of patients with 'best' and 'worst' case scenarios (i.e., those in whom all three factors apply; for those whom only one applies). Predictably, the SRs were higher for patients with all three factors than those with only one (30.5%; n=36/118, vs 5.4%; n=3/55, respectively). The number needed to treat (NNT) to obtain one complete SR in patients with all three factors was 3.3, whilst for those with only one factor the NNT was 15.8.

The results of this meta-analysis are of limited value to this report as no IFN monotherapy comparator arm is included, precluding an assessment of the marginal clinical and cost-effectiveness. Nevertheless, the results do provide some indication of predictors of SR and thus how re-treatment may be targeted to specific sub-groups of patients.

Results from our meta-analysis

The systematic reviews described above included literature published only up to November 2001. We therefore performed an additional literature search to identify studies published between then and February 2003 (see Appendix 8). This search yielded an additional 3 RCTs. The search also identified studies in which patients were re-treated with IFN + RBV but without an IFN only/IFN + placebo comparator (e.g. comparing different doses/durations of IFN +RBV) [73;79-87]. These studies were excluded as they prohibited analysis of the marginal clinical-effectiveness and cost-effectiveness of moving from IFN to IFN + RBV.

The grand total of re-treatment studies meeting our inclusion criteria was therefore 20

- 12 from the previous assessment report[88-99],
- an additional 5 from other systematic reviews[100-104]; and
- 3 from our updated February 2003 search[105-107].

Although we had relied on the previous systematic reviews as a means of identifying quality assessed relevant trials, our February 2003 search

yielded newer studies which have not been subjected to formal systematic review. We therefore performed our own meta-analysis to synthesise *all* of the available evidence. This represents the most up to date meta-analysis in this area with the largest number of RCTs, containing the biggest total number of patients re-treated (n=2144).

The proportion of patients remaining infected with HCV after re-treatment were entered into Cochrane Review Manager 4.1 software. Two separate analyses were performed.
The primary analysis included trials in which therapy was administered for 24 weeks (n= 1515). (This analysis also consisted of sub-groups of trials that included only patients who had never responded to previous IFN treatment and trials that included both non-responders and patients who had relapsed after initial response to previous IFN treatment. Two included trials[96;103] randomised and reported separately results from non-responders and relapsers. Only the non-responder data are included from these trials.)

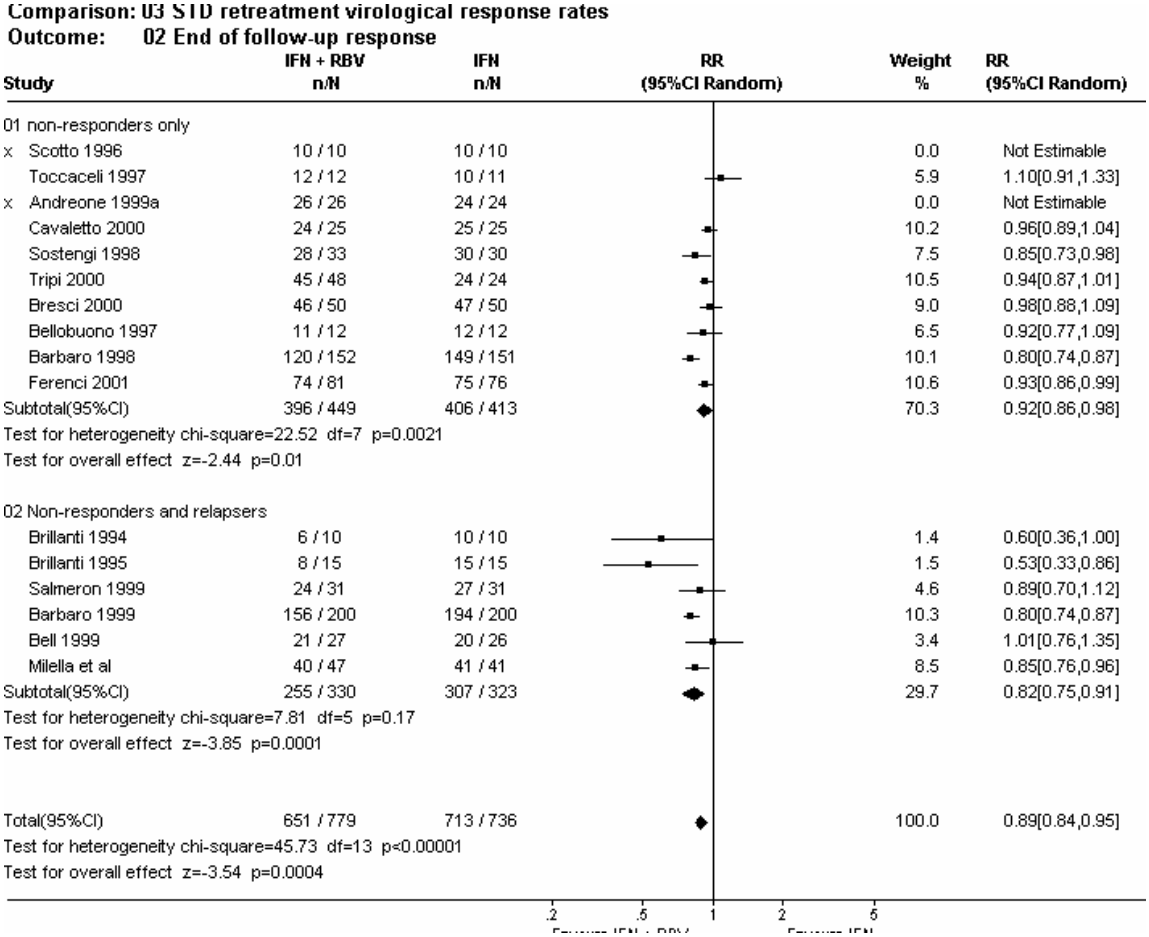
A second analysis was performed on trials with treatment durations greater than 24 weeks (n=274). When trials reported the results from intention-to-treat analyses, these results were entered into the meta-analyses. Four trials reported on-treatment analyses only and an additional 4 trials were unclear as to whether their SVR results were based on an intention-to-treat analysis. When intention-to-treat analyses were used, patients whose data were not available at follow-up were considered non-responders to treatment. Due to significant statistical heterogeneity, a random effects model was used in each of the analyses.

- The primary analysis included 16 trials in which either non-responders (10 trials) or a mix of non-responders and relapsers (6 trials) were retreated with either IFN + RBV or IFN monotherapy for 24 weeks.
- In the 10 trials that included only non-responders (which included 2 trials that recruited both non-responders and relapsers, but that randomised and reported upon the two groups separately), the meta-analysis showed that the combined relative risk was 0.92 (95% CI, 0.86 – 0.98) favouring treatment with IFN + RBV.
- Combining these ten trials together the SVR for re-treatment with IFN + RBV was 12% (95% CI, 8.8 – 14.8%) and for re-treatment with IFN was 2% (95% CI, 0.7% – 3.5%).
- For the 6 trials that included both non-responders and relapsers the combined relative risk was 0.82 (95% CI, 0.75 – 0.91) favouring treatment with IFN + RBV.
- Combining the six trials together the SVR for re-treatment with IFN + RBV was 23% (95% CI, 18.2% – 27.2%) and for re-treatment with IFN was 5% (95% CI, 2.8% – 7.9%).
- For all 16 trials taken together the combined relative risk was 0.89 (95% CI, 0.84 – 0.95) favouring treatment with IFN + RBV.
- Combining all 16 trials together the SVR was 16% (95% CI, 13.8 – 19%) for re-treatment with IFN + RBV and 3% (95% CI, 2.0 – 4.6%) for re-treatment with IFN. See Figure 5.

The effect of combined IFN and RBV treatment was greater in the trials that included both relapsers and non-responders. Among the trials reporting SVR separately for previous non-responders and relapsers, the relapsers were far more likely to achieve a sustained response in the re-treatment trial.

There was significant heterogeneity, which might be due to several differences among the trials. The trials differed in the doses of IFN given and the trials with the lower doses are displayed first within each sub-group in the figure. There do not appear to be reliably differing effects according to IFN doses. There were also small variations in RBV doses. Trials also differed in which type of IFN was used. Trials using either recombinant IFN or natural IFN were included. The nature of the previous unsuccessful treatment may also have differed among trials (e.g. IFN dose or duration).

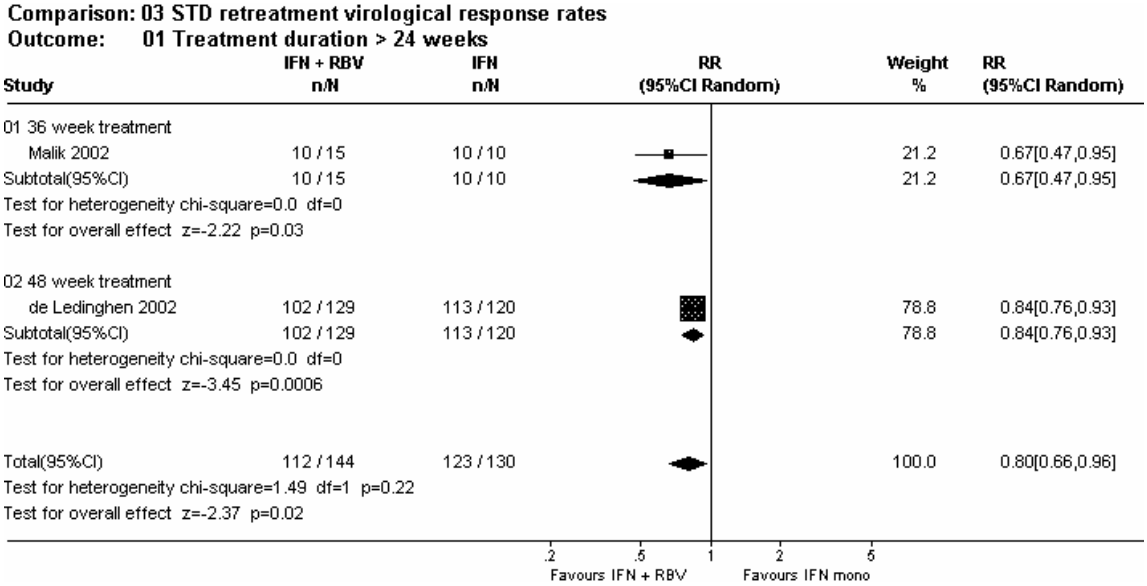
Figure 5 Relative risk for re-treatment (24 weeks)



An additional analysis was performed on two trials that continued treatment for longer than 24 weeks. The meta-analysis results for these two trials are shown in figure 6. This analysis again demonstrated an advantage of re-treatment using the combination of IFN and RBV.

- The combined relative risk was 0.80 (95% CI, 0.66 – 0.96) favouring IFN + RBV.
- The SVR for these two trials combined was 22% (95% CI, 15.4% – 29.0%) for re-treatment with IFN + RBV and 5% (95% CI, 2.2% – 10.8%) for re-treatment with IFN. These longer trials included only patients who had not responded to previous IFN monotherapy (i.e. there were no relapsers).
- In comparison with the shorter trials with non-responders, these longer trials suggest the possibility that for non-responders dual therapy of a longer duration may be more effective than a 6 month course of treatment.

Figure 6 Relative risk for re-treatment (>24 weeks)



Two trials that met our inclusion criteria were nonetheless not included in either meta-analysis because they differed significantly from other trials. One trial by Andreone, *et al.* [104] included 2 conditions testing IFN + RBV and IFN re-treatment in previous non-responders. However, the treatment was only given for 4 months. The SVR of 14% in the IFN + RBV group was similar to that seen in trials lasting for 6 months, but there were no patients with SVR in the IFN group. A trial by Pol, *et al.* [90] retreated non-responders for 12-14 months but the combined treatment with IFN and RBV lasted only 2 months and occurred between phases of RBV alone and IFN alone. Perhaps not surprisingly, the SVR in the group receiving IFN + RBV for part of their treatment was only 10%. These results suggest that dual therapy may need to be administered for some minimum period *in combination* rather than sequentially for the best effect.

3.5.3 Re-treatment with alternative interventions: amantadine

Although not within the scope of this assessment report a number of RCTs of re-treatment with various combinations of IFN, RBV and Amantadine Hydrochloride (AMA) were identified. For example, there has been evaluation of dual therapy with IFN + AMA versus IFN monotherapy[108], or AMA monotherapy[109], or IFN + placebo[110]. There has also been a head to head comparison of dual therapy with IFN + RBV against dual therapy with IFN + AMA[110], as well as re-treatment with triple therapy (IFN + RBV + AMA) versus dual therapy (IFN + RBV) [111]. Triple therapy in one RCT of 94 patients was associated with a SVR of 48% in comparison to a SVR of 5% dual therapy (IFN + RBV) [112]. A systematic review of 'Amantadine with or without interferon for chronic hepatitis C' may

potentially be conducted by the Cochrane Hepato-Biliary Group in the near future, although it is not yet clear whether this will include studies of patients who are non-responsive to prior IFN monotherapy.

3.5.4 Re-treatment: summary/discussion

- The evidence for the clinical-effectiveness of re-treatment with PEG is at present limited to conference abstracts. Preliminary results suggest end of treatment responses in 53% of patients, and SVRs only in around 20%. SVRs were significantly greater in patients who had previously failed IFN monotherapy than in those who had failed dual therapy with IFN + RBV.
- At least one RCT is likely to fully publish results of re-treatment with PEG dual therapy in the near future.
- There is a much larger evidence base for re-treatment with dual IFN + RBV, comprising a number of systematic reviews, an individual patient data meta-analysis, and our own meta-analysis encapsulating all of the available evidence.
- Results from other systematic reviews report SVRs for re-treatment with dual IFN + RBV are in the range 12-14% compared to only 2% for re-treatment with IFN monotherapy. The SVR for re-treatment with IFN + RBV is only slightly lower than the 20% SVR observed for re-treatment with PEG + RBV, although this is an indirect comparison based on a conference abstract so caution is urged in this interpretation.
- The current review meta-analysed all located RCTs that compared combination IFN + RBV therapy and IFN monotherapy in the re-treatment of non-responders and relapsers to previous IFN monotherapy. These analyses demonstrate that the risk of remaining infected with HCV is reduced by approximately 11% after 6 months of treatment. The risk reduction is slightly greater (18%) in trials that included patients who had relapsed after response to previous IFN monotherapy as well as those who had never responded to previous IFN monotherapy suggesting that re-treatment with combination therapy is slightly more effective in relapsers than in non-responders. These results are very similar to those from the other systematic reviews, however it is useful to see the differences between trials that included non-responders to previous IFN treatment versus trials with a mix of non-responders and relapsers.
- The two trials that retreated non-responders for longer than 24 weeks are new and only one of these had been included in one previous systematic review. The analysis of these trials suggests that re-treatment of non-responders with 36 or 48 weeks of IFN + RBV may be more effective than shorter durations of re-treatment resulting in a 20% reduced risk of remaining infected with HCV for IFN + RBV treatment versus IFN alone. However, as this is an indirect comparison, it should be treated with caution.
- Multi-variate analysis performed on the individual patient meta-analysis found that younger patients with normal baseline γ-

glutamyltransferase levels re-treated with a total dose of ≥ 432 MIU of IFN over a duration of (>26 weeks) are likely to derive the most benefit. A complete sustained response (i.e. both biochemical and virological) was achieved in 30.5% of patients who met this criteria, compared to only 5.4% who only met one.

The relatively lower proportion of patients who respond after re-treatment with both IFN + RBV and PEG + RBV raises the issue of what course of action should be taken for patients who have yet to respond. Shiffman (2002) [73] classified these patients according to those with advanced fibrosis or cirrhosis and those with either none or only mild degrees of fibrosis, the latter of whom are at low risk of developing cirrhosis within the next 5 to 10 years or potentially longer. For these patients long-term monitoring is recommended and re-treatment only if a potentially more effective therapy emerges. For patients at higher risk or cirrhosis and hepatic decompensation long-term maintenance therapy is recommended to improve hepatic inflammation and fibrosis. This suggestion is based on the results of trials of IFN monotherapy in which patients experienced a 40% histological response during treatment. Shiffman *et al.* later conducted an RCT which formally tested this hypothesis whereby non-responders to IFN monotherapy were randomly assigned to remain on IFN long term, or cease treatment[113]. After 2.5 years patients on maintenance therapy experienced reduced HCV RNA levels and improvements in hepatic inflammation and fibrosis, in contrast to those who ceased treatment who experienced no such benefits. The effectiveness of long term maintenance therapy with PEG IFN is the subject of the HALT-C trial as mentioned above, which is due to complete in 2006.

3.6 Treatment of patients with mild hepatitis C

Although the focus of the current report is primarily the effect of treating severe chronic hepatitis C, many patients have mild histological changes on liver biopsy and are at lower risk of developing liver-related morbidity or mortality. It has been assumed that this lower risk is outweighed by the potential risks of treating the infection. These patients, however, may be at risk of disease progression. There has been some research on responses to treatment in patients with mild disease. There are no reports of trials using pegylated interferon, but the use of non-pegylated interferon has been tested in these patients.

One Swedish trial[114] randomised 116 patients with histologically mild disease (Knodell activity score ≥1 and ≤ 6; periportal piecemeal necrosis ± bridging necrosis ≤ 3; interlobular degeneration and focal necrosis ≤ 3 and portal inflammation ≤ 4; fibrosis stage ≤ 1) to treatment using IFN α-2b (3 MIU 3x/wk) with or without RBV (1000-1200 mg/day depending on weight) for 52 weeks. Treatment was stopped according to the protocol after 6 months in 42 patients (18 in the combination group) who were still HCV-RNA positive. At follow-up (week78) there was a 54% SVR for patients on IFN + RBV and a 20% SVR for patients on IFN and placebo (p = 0.001). The SVR was significantly higher for combination therapy both

in patients with non-1 genotypes (81% vs 36%) and for genotype 1 (28% vs 4%). Viral loads were significantly lower among those patients who cleared the virus than those who were not responders in both treatment groups. Among those patients with evaluable liver biopsies, there was a significant improvement in mean histology grade score in all sustained responders independent of treatment arm. No improvement in histology was seen in those patients without SVR. All but 12 patients reported at least one adverse event, the majority being classified as mild to moderate. Treatment was discontinued in 9 patients because of side effects, three of which were classified as serious adverse events. These results suggest that combination IFN + RBV therapy is safe and effective in patients with mild disease. It is noteworthy that the SVRs achieved in this trial are higher than for some of the larger trials evaluating this therapy in patients with more severe disease. On this basis it could be argued that pegylated interferon treatment in these patients is also likely to be effective.

Further evidence for the effectiveness of treating patients with mild disease will shortly be published from the UK NHS HTA Programme funded Mild HCV trial (due to be completed in mid to late 2003). This multi-centre, randomised controlled trial recruited 205 patients and is comparing the effects of combined IFN 2b (Viraferon, 3MIU 3x/wk) + RBV (1000-1200) with no treatment. The patients are adults with mild chronic hepatitis C (Ishak necroinflammatory score < 4, fibrosis score < 3) who have not been previously treated with IFN and who do not have significant co-morbidities. Patients are being treated for 48 weeks and monitored throughout the trial. Patients are also seen for follow-up 12, 24 and 48 weeks after the end of treatment.

The trial will report on virological, histological, and biochemical response to treatment 12 months after discontinuation of therapy. The trial will also be considering the effects of genotype on response, whether early viral kinetics or host factors can predict a long-term response in combination therapy, the effect of treatment on quality of life, the cost of the treatment regimen, the potential cost savings of early treatment, and the potential cost savings of targeting therapy and avoiding ineffective therapy.

Health-related quality of life will be assessed using the SF-36 modules 12 and 13 and a validated hepatitis C disease-specific module 14. Health economic issues will be evaluated using a Socio-economic questionnaire. (These are both self-report measures.) The health-economic component is being conducted at 3 of the 12 centres (St. Mary's Hospital, London; Newcastle; and Southampton).

3.7 Results – Effectiveness of non-invasive tests for fibrosis on biopsy

If treatment for chronic hepatitis C was inexpensive and had no side-effects, it would be given to everyone infected. However there are life-diminishing treatment side-effects and risks, which have to be offset against clinical benefit, especially as not all patients respond (so that treating all patients means causing side-effects in some who will not

benefit). The cost also has to be borne in mind, because treatment is not cheap, and there are the usual opportunity cost considerations, usually reflected in a cost per QALY threshold.

The present consensus is that those with only mild liver disease, or less, should not be treated, because their rate of progression to serious disease is thought to be low and slow. Hence even leaving monetary considerations aside, the benefits of treatment are thought insufficient to justify the side-effects of treatment. This belief is partly due to a lack of evidence of the costs and benefits of treatment in mild disease, and an RCT commissioned by the UK HTA Programme is underway (see section 3.6).

The consensus is based mainly on expectations of progression to more serious liver disease. One of the evidence gaps is in the effect on quality of life of HCV infection in those with only mild liver disease. If their quality of life was reduced to the extent that treatment would achieve a cost-effective improvement in quality of life, then these patients would receive treatment, and there would be no need for liver biopsy. The evidence we need is of quality of life at three points;

- before treatment – the effect of chronic viral infection, systemic not just hepatic
- during treatment – a temporary diminution due to side-effects, for 24 or 48 weeks
- after treatment – in those who achieve sustained viral clearance, does quality of life return to normal?

One point worth noting is that in diseases of insidious onset, low grade symptoms may not be fully appreciated - the patient may not realise how unwell they felt until restored to normal health.

Hence in most places, the current consensus is that liver biopsy should be done in order to identify those in whom treatment is appropriate. This applies less to those with haemophilia, because of the risk of bleeding (Makris *et al*. 2001)[115].

Liver biopsy is not without serious though fairly rare side-effects, such as hepatic bleeding. However, it requires hospital care and associated resource use. Other options, less invasive than biopsy, have therefore been sought.

These fall into 5 groups:

- markers of inflammation such as transaminases (e.g. ALT – alanine aminotransferase).
- markers of fibrosis such as extracellular matrix tests, such as hyaluronic acid and laminin.
- cytokines and receptors such as tumour necrosis factors. Most of these are associated with fibrosis but TNF alpha is associated with inflammation but not fibrosis.
- a wide range of other tests has been tried.

- combinations (sometimes called "panels") of tests have been used, in the hope that the combination would give greater predictive value than single tests.

These were the subject of a recent high quality systematic review by Gebo *et al*. (2002) [62], on behalf of the US Agency for Healthcare Research and Quality (see section 3.3). This review included studies published up to March 2002, and thus a full systematic review of such studies need not be repeated here. The main findings were:

- the transaminases have only modest ability to predict fibrosis on liver biopsy;
- the extracellular matrix tests were of more value, with hyaluronic acid giving the best correlation, though with a wide range of sensitivity and specificity amongst studies;
- the cytokines are of less value than the extracellular matrix tests;
- panels of tests gave best results, though they may be of most use at the ends of the disease spectrum, for predicting no or only minimal fibrosis, or at the other end, the presence of cirrhosis.

However at the borderline that currently matters in clinical care, between mild and moderate liver disease, none of the above tests appeared to be adequate for decisions on treatment.

The reliability of liver biopsy was examined in an earlier (non-systematic) review by Fontana and Lok (2002) [116]. They note that a 2 cm core of liver tissue represents 1/50,000 of the whole organ. This may explain therapeutic studies which appear to show regression of changes; the post-treatment biopsy may by chance have been from a less affected section of the liver. Fontana and Lok report reasonably good inter-observer agreement amongst pathologists on fibrosis (70-90%) but less with inflammation.

Herve *et al.* (2000) [117] (a study which does not seem to have been included in the Gebo *et al.* review) examined a group of patients who had persistently normal ALTs. Compared to patients who had chronically elevated ALTs, their group had less fibrosis (mean Knodell score 3.2 versus 7.2). However, only 9% had normal liver histology, and 75% had some histological evidence of progression to chronic liver damage, ranging from mild disease to cirrhosis. Thus a persistently normal ALT may be associated with less severe liver damage, but may not be a strong enough predictor for treatment decisions.

Two studies from the British Isles report different findings when liver biopsies are repeated after 2 or more years. The different results may relate to the patients in each study.

- Albloushi *et al*. (1998) [118] found that in the cohort of Irish women infected through contaminated anti-D immunoglobulin, there was little progression seen in biopsies done 2 years apart. They also found that

the majority of women had only mild disease 19 years after infection. The average age was 46. This study also found that ALT was a poor predictor of fibrosis.

- An unpublished study from the Trent Group (Ryder *et al* 2003[120]; academic in confidence) gives details of progression as seen on follow-up liver biopsies 2 or more years apart, in a group of patients with initial mild disease, and who were therefore not treated.

(Academic in confidence material has been removed here.)

Forns *et al.* (2002) [119] (another study not included in the Gebo *et al*. review) used a panel of tests. Unlike some of the panels proposed, their panel consisted of simple and routinely collected data and tests – age, gamma GT, platelet count and cholesterol. Their cohort of patients included only 25% with significant fibrosis, and hence is a group more representative of typical patients. They used a score based on Scheuer's classification, and found that only 4% of those with a cut-off of 4.2 or less had fibrosis. About a third of patients had scores below this level. Furthermore, the small number of positive cases below the cut-off did not have serious liver disease such as cirrhosis. Hence it appears that this group could be spared biopsy since at present they are unlikely to have severe enough disease to be treated. However, they would need to be followed up.

Dienstag (2002) [120] in another recent non-systematic review also concluded that biopsy remained necessary for most patients; again, this was based on the belief that those with mild disease need not be treated. Like some other commentators, he makes the point that better treatments may become available, and that those with only mild disease may do better to wait.

One problem with assessing the value of non-invasive tests is that different studies have been based on different groups of patients, sometimes with more advanced disease. For our purposes, studies using population-based groups (hence with large numbers of patients with only mild disease) are most useful.

Treatment is currently given mainly with a view to preventing long-term liver disease. However a few studies have now reported on the extent of reduction in quality of life from chronic HCV – about 5% in the study by Siebert *et al.* (2003) [121].

In summary, the main purpose of biopsy is to distinguish those with mild disease from those with more serious liver changes. If it is shown that it is cost-effective to treat those with mild disease, then liver biopsy may become unnecessary.

Meanwhile, it looks as if the best indicators are panels of tests, preferably those which are routinely available in clinics, such as those used by Forns *et al* (2002) [119]. They may be most useful at the ends of the spectrum – i.e. for identifying those with serious liver damage who would be treated, and

those with mild disease who would not currently, at present. For patients around the current treat/don't treat margin, the consensus is that liver biopsy is still often necessary, though the balance of risks is different in those with haemophilia.

As discussed elsewhere in this review, pegylated interferon is more effective, and has fewer side-effects. Assuming that that it is also effective in patients with mild disease will tilt the balance of risk somewhat, and may reduce the need for biopsy.

3.8 Treatment of acute hepatitis C

Although the focus of the current report is on treatments for chronic hepatitis C infection, it is of interest to consider whether treatment of acute infection might be effective and therefore prevent chronic infection. The current literature search strategies were not designed to systematically uncover all studies on this question, but a recent review by Alberti *et al*. (2002) [122] considered the studies published in this area. Unfortunately, there have been no published studies identified using PEG in patients with acute HCV. Therefore, the evidence on the use of IFN will be briefly summarised.

Seventeen studies of IFN in patients with acute HCV were included in the Alberti *et al.* review[122]. Six of these were RCTs that included treated and untreated groups and four were conducted in similar patient groups with post-transfusion hepatitis. In a meta-analysis of the four trials, IFN therapy was associated with a statistically significant 29% increase in the rate of SVR relative to no treatment. These trials used an IFN dose of 3 MIU 3 times weekly for 12 weeks. More recently more aggressive treatments have been tested, but unfortunately these studies did not include control groups. Three studies ranged in size from 7 to 44 participants and used doses of IFN ranging from 5 to 10 MIU. Each study had an initial phase (or a single phase) that involved daily doses of IFN. These studies reported SVRs of 83%, 98% and 100%. Expected rates of spontaneous resolution of infection would be 30% - 50%[122]. Tolerability of IFN treatment in patients with acute infection was similar to that usually observed in chronic Hep C.

The largest of these more aggressive treatment studies by Jaeckel *et al.* [50] recruited 44 patients with acute hepatitis C infection in Germany. They received 5MIU of IFN α-2b daily for 4 weeks and then 3 times per week for an additional 20 weeks. In this study 43 of 44 (98%) of the participants demonstrated undetectable levels of HCV RNA at the end of treatment and at the end of a 24-week follow-up. Response to treatment was not affected by viral genotype, patients' sex or the mode of transmission (although the study may have been underpowered to detect such effects). One patient stopped therapy after 12 weeks because of side effects. These results suggest the possibility that chronic disease may be prevented by controlling viral replication early after infection.

These more aggressive treatment studies have been criticised on the grounds that they are prospective case series without a control group, the only comparator in the largest study being a small study of historical control patients[123]. Although, progression from acute to chronic HCV infection does occur in a majority of cases, a proportion of patients (perhaps 30% or more) would have had self-limited disease without treatment. The German study has also been criticised for the patient selection[124]. These patients were symptomatic and there is some evidence that symptomatic patients may be more likely to resolve the infection spontaneously than patients who have silent acute disease. Despite these difficulties, the possibility of preventing chronic infection may merit more attention and the use of PEG in such treatment might enhance the early viral replication suppression achieved by daily doses of IFN in studies showing the greatest effects of treatment. Because a relatively large number of patients with acute infection will spontaneously recover, the timing of when to treat acute patients would require careful consideration in order to minimise treating patients who would have recovered spontaneously.

4. Economic analysis

4.1 Review of economic studies

4.1.1 Cost-effectiveness studies of dual therapy (PEG)

A number of cost-effectiveness analyses of hepatitis C treatment have been published over recent years[125-128]. Some of these studies are based on health economic models which have been developed and revised over time to incorporate changes in health technology. For example, models were recently revised to incorporate the introduction of ribavirin to interferon alpha. Likewise, models are now being revised to incorporate the introduction of pegylated interferon, and some of these are described below.

Published data

Siebert *et al.* (2003) [121] published a cost-effectiveness analysis of the RCT of dual therapy (PEG 2b + RBV) by Manns *et al.* (2001) [41], based on a previously published Markov model[125;127]. The model was adapted to estimate the marginal cost-utility of dual therapy with PEG in comparison to dual therapy with IFN + RBV. The model projects the SVRs from each arm of the trial into 20 year risks for liver related complications in a hypothetical cohort of patients. Transition probabilities for histological progression, clinical decompensation, mode of decompensation, hepatocellular carcinoma, liver transplantation and mortality were taken from the published literature. Quality of life was estimated from a cross sectional interview survey of 348 German HCV patients using a visual analogue scale. Multi-variate regression analysis was used to derive utility weights. The patient survey was used for the base case analysis, however the EuroQol instrument and physician based estimates were used in

sensitivity analysis. Cost data were obtained from the German healthcare system with non-drug costs inflated to 2000 costs and converted from the German mark to euros. Cost-effectiveness was estimated using the incremental cost-effectiveness ratio, and the analysis adopted a societal perspective. Results were presented separately for fixed dose and weight based dosing of ribavirin, given that the trial identified a statistically significant relationship between SVR and ribavirin dosed according to body weight. Cost per QALY figures presented in this current assessment report have been converted from Euros into Sterling (at an exchange rate of £1 = €1.46). Costs were discounted at 3%.

Incremental discounted cost per QALYs are presented below (base case highlighted in bold):

- dual therapy with PEG (+ weight based RBV) in comparison to dual therapy with IFN + RBV = **£4520**
- dual therapy with PEG (+ fixed dose RBV) in comparison to dual therapy with IFN + RBV = **£8082**
- dual therapy with PEG (+ weight based RBV) in comparison to dual therapy with IFN + RBV (sensitivity analysis: utility estimate based on EuroQol) = £5479
- dual therapy with PEG (+ fixed based RBV) in comparison to dual therapy with IFN + RBV (sensitivity analysis: utility estimate based on EuroQol) = £9931
- dual therapy with PEG (+ weight based RBV) in comparison to dual therapy with IFN + RBV (sensitivity analysis: physician utility estimate) = £3356
- dual therapy with PEG (+ fixed based RBV) in comparison to dual therapy with IFN + RBV (sensitivity analysis: physician utility estimate) = £5753

These results show that in general that weight based dosing of ribavirin is more cost-effective than fixed dosing. The cost per QALY estimates for weight based dosing remained under £50, 000 Euros (around £34, 000) for a number of clinical sub-groups for whom assumptions were varied in the sensitivity analysis. For example, the incremental cost per QALY for patients with genotypes other than 2 or 3 was around £3,400 whilst for those with genotypes 2 or 3 the figure was around £10, 200. Likewise for patients with low baseline viral load the incremental discounted cost per QALY was approximately £2, 400 in comparison to £14, 300 for patients with high viral load. Sensitivity analysis estimates for fixed based dosing of RBV showed that treatment was cost-effective for clinical sub-groups, except for patients with high baseline viral load and those with genotypes 2 and 3. Again, this may reflect the high SVRs experienced by patients in this trial with these genotypes irrespective of treatment. Life expectancy increased by 3.8 years (when treated with IFN + RBV); 4.3 years (PEG with fixed RBV); and 4.9 (PEG with weight based RBV). One of the limitations of the study (as acknowledged by the authors) is the assumption that the results of weight based dosing, which was only

received by a sub-group of patients in the trial, can be applied to all patients treated.

In a cost-effectiveness analysis by Buti *et al.* (2003)[129] of PEG α-2b + RBV a Markov decision analysis model was used. The model appears to be similar to that used by Siebert *et al*. described above, and adopted the Spanish health system perspective. The demographics and virological characteristics of the patients were obtained from the Manns *et al*. study. Additional patient characteristics were considered to be the same as in previous multi-centre trials of PEG or IFN.

Four treatment strategies were considered:

1. IFN α-2b 3 MU three times per week + RBV 1000-1200 mg/day depending on body weight for 48 weeks;
2. PEG α-2b 1.5 µg/kg per week + RBV 800 mg/day for 48 weeks;
3. PEG α-2b 1.5 µg/kg per week + RBV adjusted for body weight (800-1200mg) for 48 weeks;
4. PEG α-2b 1.5 µg/kg per week + RBV adjusted for body weight (800-1200mg) for 48 weeks with patients compliant with therapy (received at least 80% of both drugs for at least 80% of treatment duration).

This analysis focused on patients with different genotypes (particularly genotype 1), the effect of different dosing methods (adjustment by body weight) and on the effects of compliance with therapy. Quality of life estimates were determined by a panel of hepatologists. The model incorporated only direct costs from the perspective of the Spanish national health system. Costs were adjusted for inflation to year 2000 values. A discount rate of 3% was applied to costs and health benefits. Cost per QALY figures from the report have been converted in the current report from Euros into Sterling at an exchange rate of £1 = €1.46.

The incremental discounted costs per QALY for PEG therapies compared with IFN + RBV therapy are presented below:

- All patients:
    - PEG + RBV 800 mg/day (fixed dose) vs IFN + RBV = £2559
    - PEG + RBV (adjusted for body weight) vs IFN + RBV = £1732
    - PEG + RBV (by body weight) + compliant with therapy vs IFN + RBV = £494
- Patients with genotype 1:
    - PEG + RBV 800 mg/day (fixed dose) vs IFN + RBV = £1750
    - PEG + RBV (adjusted for body weight) vs IFN + RBV = £1732
    - PEG + RBV (by body weight) + compliant with therapy vs IFN + RBV = £277

The incremental discounted costs per QALY for other therapy comparisons are presented below:

- All base-case patients:
    - PEG + RBV 800 mg/day (fixed dose) vs IFN + RBV = £2575
    - PEG + RBV (adjusted for body weight) vs PEG + RBV 800 mg/day (fixed dose) = £911
    - PEG + RBV (by body weight) + compliant with therapy vs PEG + RBV (adjusted for body weight) = Cost Saving

These results demonstrate that the optimal strategy is a combination of PEG α-2b (PEG α-2a was not considered in this study) and RBV adjusted to the patients' body weight for 48 weeks with good compliance to therapy. This strategy is even more cost-effective for patients with genotype 1 than for patients generally. This study did not include the possibility of stopping therapy for patients with genotype 1 who were still HCV RNA positive at week 24 or who had a less than 2-log decrease in HCV RNA at week 12.

Because of the generally slow progression of Hep C, the age at the time of initial of therapy affects the cost-effectiveness ratio of treatment. The incremental cost-effectiveness ratio increases as the age at start of treatment increases. Although a determination of what is 'cost-effective' is a subjective judgement, the age threshold for treatment remaining cost-effective increases for each therapy with a higher age threshold for treatment with PEG + RBV with good compliance.

The base-case results assumed that all patients completed 48 weeks of treatment. Sensitivity analyses considered effects of earlier treatment discontinuation in some patients as well as body weight distributions as in the clinical trials. Key probabilities of disease progression were halved or doubled and different discount rates for costs and health benefits (0% and 5%) were used. SVR rates were also modified. In all sensitivity analyses PEG + RBV with good compliance remained the most cost-effective therapy.

Unpublished data

A number conference abstracts reporting the cost-effectiveness of dual therapy with PEG 2b + RBV based on the RCT by Manns *et al.* (2001) were identified. Again, as these have not been subjected to peer review for full publication the results must be interpreted with caution.

- Wong and Nevens (2002) [130] performed a cost-utility analysis, again based on the Manns *et al.* (2001) trial, using an adapted version of the Markov model used by Siebert *et al.* (2003) above. This short publication carries the status of an 'extended abstract' and thus it is not clear if it has been fully peer reviewed. The predicted estimates in the model had previously been shown to match closely the results of natural history studies[125]. Belgian costs

were estimated in the model and the cost per QALY figures presented in this current assessment report have been converted from Euros into Sterling (at an exchange rate of £1 = €1.46). The discount rate for costs and survival was 3%. Marginal discounted cost per QALYs are presented below (base case highlighted in bold):

- dual therapy with PEG in comparison to no treatment = **£1618**
- dual therapy with PEG in comparison to dual therapy with IFN + RBV = **£4362**
- dual therapy with PEG in comparison to dual therapy with IFN + RBV (genotypes 2 & 3) = £8446
- dual therapy with PEG in comparison to dual therapy with IFN + RBV (genotypes 1, 4 or 5) = £2864

The higher cost per QALY for patients with genotypes 2 and 3 in relation to that for patients with genotypes 1, 4 or 5 probably reflects the similar SVRs for patients treated with PEG dual therapy (82%) and patients treated with IFN + RBV dual therapy (79%) in this trial.

- Wong *et al.* (2002) [131] performed a cost-utility analysis examining the incremental cost per discounted QALY (3% discount rate) associated with the following treatment options: (i) no treatment; (ii) dual therapy (IFN + RBV); (iii) dual therapy (PEG + 800mg RBV); (iv) dual therapy (PEG + >10.6mg/kg RBV). The cost-effectiveness of three different 'optimised' treatment algorithms were explored:
  - (a) discontinuing therapy in viral positive patients after 24 weeks of treatment (Stop 24);
  - (b) same criteria in Stop 24 but also limiting therapy in those with genotype 2/3 to 24 weeks (Stop 2/3);
  - (c) same criteria in Stop 2/3 but also discontinuing therapy in those viral positive or <2 log drop in viral load in non-genotype 2/3 patients after 12 weeks.

  Costs were presented as US$ and converted in this report to Sterling (£1 = $1.58).
  Compared to no treatment (option i):
  - The marginal discounted cost per QALY for option ii was £2088 (Stop 24) and £1202 (Stop 12). For options iii and iv the marginal discounted cost per QALYs were £2721 (Stop 24) and £1708 (Stop 12) and £2784 (Stop 24) and £1772 (Stop 12), respectively.
  - The marginal discounted cost per QALY for the three treatment options ranged from £632 to £1708 (Stop 24, genotype 2/3 patients). All three treatment options became cost saving even with discounting.
  - For genotype 1 patients moving the Stop 24 to the Stop 12 rule improved cost-effectiveness of treatment from £3481-£3924 to £2974-£3481.

  Compared to dual therapy (IFN + RBV) (option ii):

- the marginal discounted cost per QALY for option iii was £4746 (Stop 24) and £3291 (Stop 12), and for option iv it was £7215 (Stop 24) and £5253 (Stop 12).
- For genotypes 2/3 the cost-effectiveness of option iii improved from £28, 860 with Stop 24 to £12,151 with Stop 12, and for option iv cost-effectiveness improved from £3227 with Stop 24 to £474 with Stop 2/3.

The results show that applying treatment stopping rules in patients who have not responded can improve the cost-effectiveness of anti-viral therapy, with the 12 week stopping rule generating the lowest marginal cost per QALY.

A similar cost-utility analysis was quoted which was performed by the same team but with drug costs based on doses used and vial sizes in the UK (Wong et al. 2003). This information is academic in confidence and has therefore been removed.

4.1.2 Review of Health Related Quality of Life (HRQOL) studies

A number of studies assessing the HRQOL of patients receiving treatment with PEG, both as dual and monotherapy, were identified. These were all based on patients treated in the RCTs of pegylated interferon described in sections 3.2.2 and. 3.2.3. The majority are conference abstracts and thus caution is advised in their interpretation.

Dual therapy (unpublished data)

- Gish *et al.* (2002) [132] in a conference abstract report HRQOL data from the trial of dual therapy by Manns *et al.* (2001) [41] where patients received dual therapy with either PEG 2b + RBV or IFN 2b + RBV. Patients completed the SF-36 before, during and after treatment. Scores were higher for patients receiving PEG dual therapy at both 12 and 48 weeks of treatment, indicating better on-treatment quality of life for pegylated interferon compared to non-pegylated. The difference between the groups reached statistical significance for the pre-specified domain of 'Vitality' at 12 weeks of treatment. Improvements in scores were higher for sustained responders in comparison to non-responders whose scores did not improve.

- Hassanein *et al.* (2001) [133] reported the HRQOL data from the trial of dual therapy by Fried *et al.* (2001). Patients received PEG α-2a + RBV, IFN α-2a + RBV, or PEG α-2a + placebo and completed the SF-36 and the Fatigue Severity Scale (FSS) before, during and after treatment. During treatment those on PEG + RBV reported higher HRQOL and less fatigue than those taking IFN + RBV on all domains of the SF-36 and the FSS, with statistically significant differences in vitality, body pain, social functioning and burden of fatigue. Patients receiving PEG + placebo also had better HRQOL

than those receiving IFN + RBV for all SF-36 domains and the FSS. At the end of follow-up (72 wk) patients who had attained a virological response reported significant HRQOL improvements from baseline in all domains of the SF-36 and FSS scores with the greatest improvements in role-physical, general health, vitality, and role-emotional scales.

- A second conference abstract by Hassanein *et al.* (2002) [134] reports HRQOL benefits from patients treated with PEG α-2a + RBV versus IFN + RBV. HRQOL was assessed using the SF-36 and the FSS. This study evaluated QoL changes over a finer time scale. HRQOL scores declined from baseline to week 2 in both groups and declined further by week 12 and the remained stable through week 48. HRQOL was better for the PEG + RBV group than the IFN + RBV group at week 2 on all scales, at week 12 on 6 SF-36 domains and the FSS, and at weeks 24 and 48 on all scores. These results suggest that advantages in HRQOL for PEG + RBV emerge early and that more favourable HRQOL might reduce premature discontinuation of treatment.

Monotherapy (published data)

- Bernstein *et al.* (2002) [135] pooled HRQOL data from three open-label trials of PEG α-2a versus IFN α-2a (Zeuzem *et al*. 2000[53]; Heathcote *et al*. 2000[52]; and the unpublished trial by Pockros *et al*. (2001) [61]). In these trials the patients completed the SF-36 Health Survey and the Fatigue Severity Scale (FSS) at baseline and weeks 2, 12, 24, 48, and 72. The primary objective of the pooled analysis was to examine the relationship between SVR and HRQOL. SVR was significantly associated with changes in fatigue scores and all domains of the SF-36. The effect was primarily due to improvement in HRQOL from baseline to week 72 follow up in responders, and secondarily to HRQOL declines from baseline to week 72 among non-responders. During treatment (first 24 weeks) the patients receiving PEG reported significantly better HRQOL and less fatigue than those taking IFN in 7 of 8 SF-36 domains, both SF-36 summary scores and the FSS total and visual analogue scale scores. During the initial 24 weeks of therapy worsening fatigue scores and declines in SF-36 were significant predictors of treatment discontinuation. This analysis suggests that PEG therapy may involve less diminution of HRQOL during therapy and impact on adherence to therapy.

Monotherapy (unpublished data)

- A report by Rasenack *et al.* (2003) [136] considered HRQOL within the Zeuzem *et al.* trial (2000) [53]. In this trial 531 patients were randomized to PEG α-2a or IFN α-2a. Again, HRQOL was assessed using the SF-36 and the FSS. At weeks 2 and 12 HRQOL

was significantly better in the PEG group in 7 of 8 domains and both summary scores of the SF-36. At weeks 2, 12, and 24 patients receiving PEG had significantly less disabling fatigue than those receiving IFN.

- Another conference abstract (Feagan *et al.* (2000) [137]) reported changes in HRQOL of PEG 2b, based on the trial by Lindsay *et al.* (2001) [51]. The primary outcome was the SF-36 'Vitality' scale. During treatment patients receiving 0.5 µg/kg reported significantly better HRQOL than patients receiving IFN (this was consistent with the lower incidence of adverse events in this group). The difference between these groups in the change from baseline Vitality score remained at the end of treatment. However, there was no difference in HRQOL between patients receiving 1.0 µg/kg of PEG and those receiving IFN. HRQOL scores were slightly worse for patients receiving 1.5 µg/kg of PEG, and during follow-up all SF-36 scales for all treatment groups returned to pre-treatment values.

In summary the main findings from these studies are:

- Reported HRQOL, as measured using the SF-36 and Fatigue Severity Scale during treatment is generally higher for patients receiving PEG than those receiving IFN, both as dual therapy and monotherapy. This may facilitate improved patient compliance with therapy.
- There is a significant association between sustained response and improved HRQOL, consistent with previous studies.

4.2. Methods for economic analysis

This economic evaluation follows the principles of a cost-utility analysis. The perspective taken is that of the NHS but assessing not only clinical effects but also gains in length of life and quality of life, in a wide social perspective. Thus, costs for treatment are not only seen in a budget perspective but also in relation to the improved or maintained quality of life the treatment can achieve. The analysis follows the framework set out by The National Institute for Clinical Excellence (NICE) [138] in the guidelines for manufacturers and sponsors. Other principal sources include Drummond *et al.* (1997) [139], as well as earlier literature in the area.

A cost-effectiveness spreadsheet model originally developed by the Scottish Health Purchasing Information Centre (SHPIC)[c] and used in the previous assessment report was updated and used for the calculation of costs and benefits[d]. The model follows a hypothetical cohort of 1000 individuals with chronic hepatitis C infection over a 30 year period. The average age at diagnosis is 36 years. It aims to predict the natural history of the disease, the health states through which the cohort passes, how long

[c] http://www.nhsconfed.org/Scotland/shpic/

[d] Available on request

they spend in each state, and the NHS costs of treating a patient in each state. The health states, or stages, of the model are:

- chronic hepatitis C
- progression to cirrhosis
- development of ascites
- development of variceal bleeds
- development of hepatic encephalopathy
- progression to hepatocellular cancer (HCC)
- liver transplantation
- death

The options in the original SHPIC report were:

- No treatment (except symptomatically)
- Interferon monotherapy for three months, then a further nine months for responders
- Dual therapy with IFN + RBV for six months

The no treatment option was based upon projected natural history events over a 30 year period as derived from the published literature and clinical consensus (further details in Appendix 9). Disease progression in this comparator was based upon published literature and clinical consensus.

The options and assumptions were then revised in the previous assessment report with the addition of a fourth option, dual therapy for 12 months, to reflect current practice:

- No treatment (except symptomatically)
- Interferon monotherapy for 12 months
- Dual therapy with IFN + RBV for 6 months
- Dual therapy with IFN + RBV for 12 months

See Appendix 9 for a list of assumptions in the model.

For the current report the options have been further revised to reflect the treatment comparators in the published RCTs of pegylated interferon

- no treatment (except symptomatically)
- dual therapy (interferon alpha and ribavirin) for 48 weeks
- dual therapy (pegylated interferon and ribavirin) for 48 weeks
- monotherapy (interferon alpha) for 48 weeks, or for shorter periods if published data are available
- monotherapy (pegylated interferon) for 48 weeks, or for shorter periods if published data are available.

Note that even though none of these trials includes a no treatment arm, this comparator has been retained as a baseline, to estimate the incremental cost-effectiveness of moving from no active treatment to pegylated

interferon which would be likely to reflect practice for newly diagnosed untreated patients.

4.2.1. Estimation of net benefits

In theory, the benefits of hepatitis C treatment can be estimated using life years gained (LYG) or intermediary clinical manifestations such as cirrhosis of the liver, but quality of life, as discussed in section 4.1.2, is an important consideration in hepatitis C. For this reason we have chosen to use the cost-utility technique which measures the outcomes of treatment in terms of health related quality-of-life (HRQOL).

The concept of HRQOL is often measured by pre-calibrated questionnaires. For instance, a number of the studies described in section 4.1.2 report results from the SF-36 questionnaire. Another way is to compare quality of life to monetary values or length of life. This is done in the willingness-to-pay approach, or the time-trade-off technique. Standard gamble is another method. It uses the respondents' direct perceptions about probabilities to form values. Although it is considered to be high quality it may be difficult to comprehend by the respondents.

A second problem is that it is often impractical, expensive, and sometimes impossible to ask patients about their true quality-of-life values. Examples of such patient groups are young children or those with severe mental health problems. In the current report most of the HRQOL values used are taken from literature. They have been estimated using consensus-based exercises such as the Delphi technique, in which a group of hepatologists have been asked to estimate the HRQOL values of patients in certain hypothetical conditions (i.e. chronic hepatitis C; cirrhosis, etc)[125;127;140-142].

All HRQOL values have been converted to QALYs (Quality Adjusted Life Years) and the long-term consequences of reduced quality of life due to hepatitis have been discounted to present value as outlined below.

As long term results of clinical trials and natural history studies are not available, a number of assumptions about disease progression over time have been made in the form of annual transition probabilities. Recent studies suggest an increasing, non-linear progression for those infected at an older age (see Appendix 9). However, there are no data that could be entered into the present model to support this indication. The effect of a moderate progressive element would have little effect on the overall results due to the discounting of costs and effects. The costs over 30 years reduces to about 17% of their value when discounting of 6% is applied. Benefits were discounted at 1.5% and over the 30 years they are reduced to a present value of about 60%.

SVRs following anti-viral treatment have been entered into the model from our meta-analysis of the key RCTs for the primary base case analysis. The RCTs identified a number of prognostic factors (e.g. genotype, baseline viral load) which are predictors of sustained viral response. Therefore sub-group analyses were performed, whereby SVRs from the RCTs were entered into the model, to examine how the incremental cost/QALY varies according to these factors. Caution is advised when interpreting these results as some of the sub-groups contained low numbers of patients.

4.2.2. Estimation of net costs

Cost data from the literature are of uncertain quality. Data often come from charges to insurance companies and include elements of profit. Some data include administratively distributed non-direct costs which do not reflect the true resource use needed for an HTA study. Therefore, as far as possible, marginal cost data from the NHS have been used. The basis of cost estimates are the direct treatment costs and costs for equipment and direct patient administration. Costs for organisation and general administration are not included. The reason is that the choice of treatment method should be based on comparable costs and different hospitals have different ways of organising the care. Some hospitals use special treatment units, and there are also different ways of distributing costs for supporting care and administration. In addition the organisational costs should not vary whether pegylated or non-peg is used. The incremental cost-effectiveness, that is, the difference in costs between one treatment method and another needs, therefore, to be separated from such confounding cost elements.

Information on investigation, monitoring and treatment costs were provided by the Finance Department of Southampton University Hospitals Trust (see Appendix 10). The opportunity, marginal and incremental cost principles will concentrate on the differences between direct operative costs of the activities concerned. Capital costs are not included in the analysis as in most cases they will stay unchanged when moving from one non-pegylated to pegylated interferon but they are also in many cases funded from other sources than the NHS operative costs. Overhead costs pose a similar problem. If the capital budget is annuitized and transferred to the operating budget, the costs of, for instance, buildings and expensive equipment would have turned up as a part of the overhead cost, fixed over time and also unchanged with the number of patient consultations. Other such fixed costs are those of general administration, and transferred costs from departments serving other departments rather than patients directly (often named ‘indirect costs’ in the accounts).

Drug costs were taken from the British National Formulary (BNF) (Issue 44). Drug costs for PEG were based on 180µg per week (non-weight based dosing, PEG 2a); costs for IFN were based on a dose of 3MIU 3 x per week, and costs for RBV were based on 1200mg per day. Costs were discounted at the rate of 6%.

The literature does not explicitly discuss costs and effects for patients with haemophilia. It may very well be that they are more expensive to treat (e.g. more in-patient stays for liver biopsy), but we have no basis for specific assumptions on such costs or effects, positive or negative.

4.2.3. Estimation of cost-effectiveness

Dual therapy

Table 16 presents incremental discounted cost-utility estimates for the base case (i.e. all patients) for PEG dual therapy, based on the cohort of 1000 patients in the model. SVRs are from our pooled analyses of the Manns *et al.* and Fried *et al.* trials (see section 3.2.2). The incremental cost/QALY for no active treatment compared to 48 weeks of PEG dual therapy is £6,045. IFN dual therapy for 48 weeks compared to PEG dual therapy for 48 weeks generated a cost per QALY of £12,123.

Table 16 Incremental discounted cost-utility for dual therapy (base case)

	Total discounted costs	**Discounted QALYs**	**Additional costs**	**QALYs saved**	**Net cost / QALY saved**
No active treatment compared to PEG dual therapy (48 wks)					
No tx	£2,054,290	21,464	-	-	-
Dual tx (PEG + RBV)	£13,862,982	23,417	£11,808,692	1,953	£6,045
IFN Dual therapy (48 wks) compared to PEG dual therapy (48 wks)					
Dual tx (IFN+ RBV)	£9,987,505	23,098	-	-	-
Dual tx (PEG + RBV)	£13,862,982	23,417	£3,875,478	320	£12,123

Based on SVRs from meta-analysis

Results of the sub-group analyses for dual therapy are presented below. In general, cost/QALY estimates for no active treatment compared to PEG dual therapy were lower than IFN dual therapy compared to PEG dual therapy.

Table 17 presents the incremental discounted cost-utility sub-group estimates for patients treated with dual therapy stratified by genotype (the RCTs from which efficacy data are taken are indicated in parenthesis). The most favourable estimates are for genotype 2 and 3 patients treated with dual therapy in comparison to no active treatment, where the incremental discounted cost/QALY ratios were £3,866 (based on the Manns *et al*. trial) and £4,216 (based on the Fried *et al*. trial). When comparing IFN dual therapy to PEG dual therapy in these patients estimates were £37,578 and £7,051 and for the two trials respectively. In Manns *et al*. there was only a marginal difference in SVRs for PEG and IFN treated genotype 2 and 3 patients (82% vs 79%), which may explain the high cost per QALY. It is also worth noting that genotype 2 and 3 patients would not necessarily receive 48 weeks of IFN dual therapy in

practice. Thus a more appropriate comparison would be 24 weeks of IFN dual therapy versus 24 of PEG dual therapy. Such comparisons have not been made in the currently published RCTs of PEG treatment, although unpublished data are available (commercial in confidence section removed).

Table 17 Incremental discounted cost-utility for dual therapy (sub-group analysis - genotype)

	Total discounted costs	**Discounted QALYs**	**Additional costs**	**QALYs saved**	**Net cost / QALY saved**
No active treatment compared to PEG dual therapy (48 wks) Genotype 1 (Fried et al.)					
No tx	£2,054,290	21,464	-	-	-
Dual tx (PEG + RBV)	£14,046,070	23,098	£11,991,780	1,634	£7,340
IFN Dual therapy (48 wks) compared to PEG dual therapy (48 wks) Genotype 1 (Fried et al.)					
Dual tx (IFN + RBV)	£10,192,934	£22,743	-	-	-
Dual tx (PEG + RBV)	£14,046,070	£23,098	£3,853,136	355	£10,848
No active treatment compared to PEG dual therapy (48 wks) Genotype 2/3 (Fried et al.)					
No tx	£2,054,290	21,464	-	-	-
Dual tx (PEG + RBV)	£13,435,778	24,163	£11,381,488	2,699	£4,216
IFN Dual therapy (48 wks) compared to PEG dual therapy (48 wks) Genotype 2/3 (Fried et al.)					
Dual tx (IFN+ RBV)	£9,679,361	23,631	-	-	-
Dual tx (PEG + RBV)	£13,435,778	24,163	£3,756,417	533	£7,051
No active treatment compared to PEG dual therapy (48 wks) Genotype 2/3 (Manns et al.)					
No tx	£2,054,290	21,464	-	-	-
Dual tx (PEG + RBV)	£13,313,719	24,377	£11,259,429	2,913	£3,866
IFN Dual therapy (48 wks) compared to PEG dual therapy (48 wks) Genotype 2/3 (Manns et al.)					
Dual tx (IFN+ RBV)	£9,309,589	24,270	-	-	-
Dual tx (PEG + RBV)	£13,313,719	24,377	£4,004,130	107	£37,578
No active treatment compared to PEG dual therapy (48 wks) Genotype 4, 5 or 6 (Manns et al.)					
No tx	£2,054,290	21,464	-	-	-
Dual tx (PEG + RBV)	£13,964,698	23,240	£11,910,408	1,776	£6,707
IFN Dual therapy (48 wks) compared to PEG dual therapy (48 wks) Genotype 4, 5 or 6 (Manns et al.)					
Dual tx (IFN+ RBV)	£10,151,848	22,814	-	-	-
Dual tx (PEG + RBV)	£13,964,698	23,240	£3,812,850	426	£8,946

Tables 18 and 19 present the incremental discounted cost-utility sub-group estimates for patients treated with dual therapy according to baseline viral load, and baseline viral load stratified according to genotype, respectively. The lowest estimate, £3,921, was for no active treatment compared to dual therapy with PEG in patients with low baseline viral load and genotype 2/3. Predictably, the highest estimate, £13,701, was for IFN dual therapy compared to PEG dual therapy in patients with high baseline viral load and genotype 1.

Table 18 Incremental discounted cost-utility for dual therapy (sub-group analysis – baseline viral load)

	Total discounted costs	Discounted QALYs	Additional costs	QALYs saved	Net cost / QALY saved
No active treatment compared to PEG dual therapy (48 wks) high baseline viral load (Fried et al.)					
No tx	£2,054,290	21,464	-	-	-
Dual tx (PEG + RBV)	£13,903,669	£23,346	£11,849,378	1,882	£6,295
IFN Dual therapy (48 wks) compared to PEG dual therapy high baseline viral load (48 wks) (Fried et al.)					
Dual tx (IFN+ RBV)	£10,090,219	22,920	-	-	-
Dual tx (PEG + RBV)	£13,903,669	23,346	£3,813,449	426	£8,947
No active treatment compared to PEG dual therapy (48 wks) low baseline viral load (Manns et al.)					
No tx	£2,054,290	21,464	-	-	-
Dual tx (PEG + RBV)	£13,395,092	£24,234	£11,340,802	2,770	£4,094
IFN Dual therapy (48 wks) compared to PEG dual therapy (48 wks) low baseline viral load (Manns et al.)					
Dual tx (IFN+ RBV)	£9,782,076	23,453	-	-	-
Dual tx (PEG + RBV)	£13,395,092	24,234	£3,613,016	781	£4,624

Table 19 Incremental discounted cost-utility for dual therapy (sub-group analysis – baseline viral load and genotype)

	Total discounted costs	Discounted QALYs	Additional costs	QALYs saved	Net cost / QALY saved
No active treatment compared to PEG dual therapy (48 wks) high baseline viral load + Genotype 1					
No tx	£2,054,290	21,464	-	-	-
Dual tx (PEG + RBV)	£14,147,785	22,920	£12,093,495	1,456	£8,305
IFN Dual therapy (48 wks) compared to PEG dual therapy (48 wks) high baseline viral load + Genotype 1					
Dual tx (IFN+ RBV)	£10,254,562	22,636	-	-	-
Dual tx (PEG + RBV)	£14,147,785	22,920	£3,893,223	284	£13,701
No active treatment compared to PEG dual therapy (48 wks) high baseline viral load + Genotype 2/3					
No tx	£2,054,290	21,464	-	-	-
Dual tx (PEG + RBV)	£13,476,464	24,092	£11,422,174	2,628	£4,346
IFN Dual therapy (48 wks) compared to PEG dual therapy (48 wks) high baseline viral load + Genotype 2/3					
Dual tx (IFN+ RBV)	£9,740,990	23,524	-	-	-
Dual tx (PEG + RBV)	£13,476,464	24,092	£3,735,474	568	£6,573
No active treatment compared to PEG dual therapy (48 wks) low baseline viral load + Genotype 1					
No tx	£2,054,290	21,464	-	-	-
Dual tx (PEG + RBV)	£13,842,639	23,453	£11,788,349	1,989	£5,927
IFN Dual therapy (48 wks) compared to PEG dual therapy (48 wks) low baseline viral load + Genotype 1					
Dual tx (IFN+ RBV)	£10,049,133	22,991	-	-	-
Dual tx (PEG + RBV)	£13,842,639	23,453	£3,793,506	462	£8,216

No active treatment compared to PEG dual therapy (48 wks) low baseline viral load + Genotype 2/3					
No tx	£2,054,290	21,464	-	-	-
Dual tx (PEG + RBV)	£13,334,062	24,341	£11,279,772	2,877	£3,921
IFN Dual therapy (48 wks) compared to PEG dual therapy (48 wks) low baseline viral load + Genotype 2/3					
Dual tx (IFN+ RBV)	£9,597,190	23,773	-	-	-
Dual tx (PEG + RBV)	£13,334,062	24,341	£3,736,873	568	£6,576

Based on SVRs from Fried *et al.*

Table 20 presents incremental cost-utility estimates for low or high doses of ribavirin, whilst Table 21 presents incremental cost-utility estimates for low or high doses of ribavirin, stratified according to genotype. To recap, Manns *et al*. reported that the SVR was higher in all groups when the dose of RBV was greater than 10.6 mg/kg of bodyweight (i.e. above 800mg/day). The most favourable estimate, £1,987, was for patients with genotypes 2 and 3 treated with the lower dose of RBV, in comparison to dual therapy with IFN. The least favourable estimate, £13,734, was for genotypes 2 and 3 treated with the higher dose of RBV, in comparison to dual therapy with IFN. The difference in estimates for patients with this genotype might be explained by the fact that for the lower RBV dose sub-group the difference in SVR between PEG dual therapy and IFN dual therapy was much greater (29%) than for the higher RBV dose sub-group (8%), thus generating more QALYs.

Table 20 Incremental discounted cost-utility for dual therapy (sub-group analysis – ribavirin dose adjustments)

	Total discounted costs	**Discounted QALYs**	**Additional costs**	**QALYs saved**	**Net cost / QALY saved**
No active treatment compared to PEG dual therapy (48 wks) RBV dose ≤10.6 mg/kg (i.e. ≤ 800mg)					
No tx	£2,054,290	21,464	-	-	-
Dual tx (PEG + RBV)	£12,541,978	23,240	£10,487,688	1,776	£5,906
IFN Dual therapy (48 wks) compared to PEG dual therapy (48 wks) RBV dose ≤10.6 mg/kg (i.e. ≤ 800mg)					
Dual tx (IFN+ RBV)	£10,377,820	22,423	-	-	-
Dual tx (PEG + RBV)	£12,541,978	23,240	£2,164,158	817	£2,649
No active treatment compared to PEG dual therapy (48 wks) RBV dose >10.6 mg/kg (i.e. > 800mg)					
No tx	£2,054,290	21,464	-	-	-
Dual tx (PEG + RBV)	£13,740,924	23,631	£11,686,634	2,167	£5,394
IFN Dual therapy (48 wks) compared to PEG dual therapy (48 wks) RBV dose >10.6 mg/kg (i.e. > 800mg)					
Dual tx (IFN+ RBV)	£9,966,962	23,133	-	-	-
Dual tx (PEG + RBV)	£13,740,924	23,631	£3,773,962	497	£7,589

Table 21 Incremental discounted cost-utility for dual therapy (sub-group analysis – ribavirin dose adjustments stratified by genotype)

	Total discounted	**Discounted QALYs**	**Additional costs**	**QALYs saved**	**Net cost / QALY**

	costs				saved
No active treatment compared to PEG dual therapy (48 wks) RBV dose ≤10.6 mg/kg (i.e. ≤ 800mg) in genotype 1					
No tx	£2,054,290	21,464	-	-	-
Dual tx (PEG + RBV)	£12,786,095	22,814	£10,731,805	1,350	£7,951
IFN Dual therapy (48 wks) compared to PEG dual therapy (48 wks) RBV dose ≤10.6 mg/kg (i.e. ≤ 800mg) in genotype 1					
Dual tx (IFN+ RBV)	£10,521,620	22,174	-	-	-
Dual tx (PEG + RBV)	£12,786,095	22,814	£2,264,475	639	£3,542
No active treatment compared to PEG dual therapy (48 wks) RBV dose >10.6 mg/kg (i.e. > 800mg) in genotype 1					
No tx	£2,054,290	21,464	-	-	-
Dual tx (PEG + RBV)	£14,005,384	23,169	£11,951,094	1,705	£7,010
IFN Dual therapy (48 wks) compared to PEG dual therapy (48 wks) RBV dose >10.6 mg/kg (i.e. > 800mg) in genotype 1					
Dual tx (IFN+ RBV)	£10,234,019	22,672	-	-	-
Dual tx (PEG + RBV)	£14,005,384	23,169	£3,771,364	497	£7,584
No active treatment compared to PEG dual therapy (48 wks) RBV dose ≤10.6 mg/kg (i.e. ≤ 800mg) genotype 2/3					
No tx	£2,054,290	21,464	-	-	-
Dual tx (PEG + RBV)	£11,952,029	24,270	£9,897,738	2,806	£3,527
IFN Dual therapy (48 wks) compared to PEG dual therapy (48 wks) RBV dose ≤10.6 mg/kg (i.e. ≤ 800mg) in genotype 2/3					
Dual tx (IFN+ RBV)	£9,905,333	23,240	-	-	-
Dual tx (PEG + RBV)	£11,952,029	24,270	£2,046,696	1,030	£1,987
No active treatment compared to PEG dual therapy (48 wks) RBV dose >10.6 mg/kg (i.e. > 800mg) genotype 2/3					
No tx	£2,054,290	21,464	-	-	-
Dual tx (PEG + RBV)	£13,191,661	24,590	£11,137,371	3,126	£3,563
IFN Dual therapy (48 wks) compared to PEG dual therapy (48 wks) RBV dose >10.6 mg/kg (i.e. > 800mg) in genotype 2/3					
Dual tx (IFN+ RBV)	£9,289,046	24,305	-	-	-
Dual tx (PEG + RBV)	£13,191,661	24,590	£3,902,615	284	£13,734

Based on SVRs from *Manns et al.*

A sensitivity analysis was performed to examine the extent to which the cost-utility estimates differ according to variations in costs and assumptions. Table 22 shows estimates generated by varying the SVR according to the 95% Confidence Interval around the pooled estimate in our meta-analysis. It is useful to estimate cost-utility according to SVR rates at the lower end of the interval as it has been suggested that, for interferon monotherapy at least, response rates in practice can be lower than found in clinical trials. The highest incremental discounted cost/QALY, £37,611, was for the lower PEG SVR and higher IFN SVR (i.e. the smallest difference between groups). In contrast, the lowest estimate was for the higher PEG SVR and lower IFN SVR at £7,060 (i.e. the largest difference between the two treatments).

Table 22 Sensitivity analysis – variations in SVR (dual therapy)

Cost- utility estimates according to varying SVR, IFN dual therapy compared to PEG dual therapy

		IFN+RBV SVR	
		43%	**49%**
PEG+RBV SVR	**52%**	£12,152	£37,611
	58%	£7,060	£12,152

Table 23 shows differences in cost-utility estimates according to variations in the discount rate for costs and benefits. Predictably, estimates are lower at the 0%

Table 23 Sensitivity analysis – variations in discount rate (dual therapy)

Cost-utility estimates according to varying discount rate from 0 to 6%. (costs/benefits)				
	0/0%	**3.5/3.5%**	**6/1.5%**	**6/6%**
No tx to dual PEG	£4,132	£7,996	£6,049	£11,628
Dual IFN to dual PEG	£8,846	£16,335	£12,152	£23,357

Table 24 illustrates how the estimates vary according to variations in drug costs. Again, the lowest estimates correspond to the lower drug cost variation. The cost for the pharmaceuticals are the most important part of the direct treatment costs. Different hospitals/trusts have been able to negotiate different discounts from pharmaceutical companies and the list prices in the BNF do probably not reflect the true costs. We have no firm data, however, about the deviations from the true cost. We have chosen to vary drug cost plus and minus 50% to see how the variation reflects in the final results.

Table 24 Sensitivity analysis – variations in drug costs (dual therapy)

Range of incremental cost-utility ratio, varying drug costs ±50%		
Drug cost	**minus 50%**	**plus 50%**
No tx to dual PEG	£2,736	£9,363
Dual IFN to dual PEG	£5,787	£18,517

Early stopping rules

The cost-utility of stopping treatment in patients who had not responded after 12 weeks was investigated. Early studies of patients treated with non-pegylated interferon monotherapy showed that patients who remained HCV RNA positive at 12 weeks were unlikely to achieve a SVR. In contrast, later trials of dual therapy with IFN and RBV found that many patients who achieved a SVR had been viral positive at 12 weeks. Thus 24 weeks became the standard threshold for deciding whether or not a patient should cease or continue treatment. Nevertheless, kinetic studies suggested that viral response could be assessed at earlier time points using quantitative assays for HCV RNA. As described in section 3.2.2, Davis *et al.* pooled data from the dual PEG trials by Fried *et al.* and Manns *et al.* to identify how many patients achieved a viral response at 12 weeks, and of these, how many went on to achieve an SVR. (Note that only patients

treated with PEG dual therapy were analysed, as opposed to patients treated with the comparator, IFN dual therapy, thus prohibiting assessment of the incremental cost-utility between these two treatments in the context of stopping rules). The main results were:

- Of the 965 patients analysed 646 were genotype 1; 277 were genotype 2/3; and 42 had another (undefined) genotype.
- 778 (81%) of the 965 achieved a 12 week viral response (all but one of whom were genotype 2/3 patients; the remaining 502 comprising mostly genotype 1 patients, although exact figures are not specified – it is likely that some of these were genotype 4 patients).
- 529 patients (55%) in total achieved a SVR (283 genotype 1; 227 genotype 2/3; and 19 other genotype).
- Of the 187 (19%) patents who failed to respond at 12 weeks only 3 (2%) had an SVR. If a 12 week stopping rule had been initiated only 3 of the 529 patients who had an SVR would have had treatment stopped prematurely (thus a negative predictive value of 98.4%)

What this study adds, therefore, is evidence that nearly all genotype 2/3 patients achieve an early viral response. Whilst a large proportion of genotype 1 patients also achieve an early response, the pool of patients not responding is comprised almost entirely of patients with genotype 1, and who are very unlikey to respond with continued treatment. Davis suggested that withdrawing the 19% of patients at 12 weeks who haven't responded (and who are unlikely to respond) will reduce treatment costs by 16% (although no data are provided to illustrate how this figure was calculated).

The SVR figures derived by Davis were applied to the cost-utility model of 1000 hypothetical patients in the current report.

- If we assume that the 19% of patients (most of whom are genotype 1) without an early viral response leave treatment after 12 weeks, and nothing else changes except savings in treatment costs, the total discounted costs will be £11,683,203, with a cost saving of £2,188,772 (15.7%).
- Treating the 19% of patients who failed to respond by week 12 for the remaining 36 weeks (bearing in mind that 2% of them achieve a SVR) will result in total discounted costs of £14, 968, 965 and a total of 21, 521 QALYs. When comparing this to no active treatment (total discounted costs of £2, 054, 290 and total QALYs 21,464) the incremental discounted cost per QALY will be £226, 573.

These data therefore illustrate that excluding from dual therapy non-responding genotype 1 patients after 12 weeks can lead to savings of around 16%, a similar figure to that quoted by Davis. It is important to note, however, that whilst the pool of non-responders is comprised of

mostly genotype1 patients, some patients with this genotype do achieve an earluy viral response.

Dual therapy - additional analyses based on unpublished data

(Additional analyses were performed to estimate the cost-utility for shorter durations of treatment (i.e. 24 weeks) in comparison with longer durations (i.e. 48 weeks), and stratified according to genotype, based on unpublished data that are commercial in confidence and have therefore been removed. 6 Tables covering 4 pages have been omitted.)

Monotherapy

To recap, the cost-utility of monotherapy was estimated given that not all patients are can tolerate ribavirin. Table 31 presents incremental discounted cost-utility estimates for the base case (i.e. all patients) for PEG monotherapy based on the cohort of 1000 patients in the model. SVRs are from our meta-analyses of the monotherapy trials (see section 3.2.3). The incremental cost per QALY for no active treatment compared to 48 weeks of PEG monotherapy is £6,484. Comparing 48 weeks of IFN monotherapy with 48 weeks of PEG monotherapy generates a cost per QALY of £8,404.

Table 25 Incremental discounted cost-utility for monotherapy (base case)

	Total discounted costs	**Discounted QALYs**	**Additional costs**	**QALYs saved**	**Net cost / QALY saved**
No active treatment compared to PEG monotherapy (48 wks)					
No tx	£2,054,290	21,464	-	-	-
Monotherapy PEG	£9,193,460	22,565	£7,139,170	1,101	£6,484
IFN monotherapy (48 weeks) compared to PEG monotherapy (48 weeks)					
Monotherapy IFN	£4,118,689	21,961	-	-	-
Monotherapy PEG	£9,193,460	22,565	£5,074,771	604	£8,404

Based on SVRs from meta-analysis

As with the dual therapy analyses presented above, sub-group analyses were conducted for monotherapy the results of which are presented below. Table 32 presents the incremental discounted cost-utility estimates for patients treated with monotherapy stratified by genotype.

Table 26 Incremental discounted cost-utility for monotherapy (sub-group analysis - genotype)

	Total discounted costs	**Discounted QALYs**	**Additional costs**	**QALYs saved**	**Net cost / QALY saved**
No active treatment compared to PEG monotherapy (48 wks) in Genotype 1					
No tx	£2,054,290	21,464	-	-	-
Mono tx PEG	£9,542,689	21,961	£7,488,399	497	£15,060

IFN monotherapy (48 weeks) compared to PEG monotherapy (48 weeks) Genotype 1					
Mono tx IFN	£4,283,033	21,677	-	-	-
Mono tx PEG	£9,542,689	21,961	£5,259,657	284	£18,510
No active treatment compared to PEG monotherapy (48 wks) in Genotype 2/3					
No tx	£2,054,290	21,464	-	-	-
Mono tx PEG	£8,823,688	£23,204	£6,769,398	1,740	£3,890
IFN monotherapy (48 weeks) compared to PEG monotherapy in Genotypes 2/3					
Mono tx IFN	£3,831,089	22,458	-	-	-
Mono tx PEG	£8,823,688	23,204	£4,992,599	746	£6,693
No active treatment compared to PEG monotherapy (48 wks) in Genotype 4, 5 or 6					
No tx	£2,054,290	21,464	-	-	-
Mono tx PEG	£8,597,716	23,595	£6,543,426	2,131	£3,070
IFN monotherapy (48 weeks) compared to PEG monotherapy (48 wks) in Genotypes 4, 5 or 6					
Mono tx IFN	£4,406,290	21,464	-	-	-
Mono tx PEG	£8,597,716	23,595	£4,191,426	2,131	£1,967

All SVRs from Lindsay *et al*.

Tables 33 and 34 present the incremental discounted cost-utility estimates for patients treated with monotherapy according to baseline viral load, and baseline viral load stratified according to genotype, respectively. As was the case with dual therapy the highest estimates were for patients with genotype 1 and high baseline viral load, in the range £29,963 to £30,701. The lowest incremental cost per QALY was for patients with genotypes 2 and 3 and low baseline viral load in the range £2,641 to £4,194. These estimates appear to correspond with what one would expect for harder to treat patients (i.e. genotype 1 and high baseline viral load) and patients with a better prognosis (i.e. genotypes 2 and 3 and low baseline viral load).

Table 27 Incremental discounted cost-utility for monotherapy (sub-group analysis – baseline viral load)

	Total discounted costs	**Discounted QALYs**	**Additional costs**	**QALYs saved**	**Net cost / QALY saved**
No active treatment compared to PEG monotherapy (48 wks) high viral load					
No tx	£2,054,290	21,464	-	-	-
Mono tx PEG	£9,357,803	22,281	£7,303,513	817	£8,941
IFN monotherapy (48 weeks) compared to PEG monotherapy (48 wks) high viral load					
Mono tx IFN	£4,221,404	21,784	-	-	
Mono tx PEG	£9,357,803	22,281	£5,136,399	497	£10,329
No active treatment compared to PEG monotherapy (48 wks) in low viral load					
No tx	£2,054,290	21,464	-	-	-
Mono tx PEG	£9,070,203	22,778	£7,015,913	1,314	£5,339
IFN monotherapy (48 weeks) compared to PEG monotherapy (48 wks) low viral load					
Mono tx IFN	£4,303,576	21,642	-	-	-
Mono tx PEG	£9,070,203	22,778	£4,766,627	1,137	£4,194

All SVRs from Heathcote *et al.*

Table 28 Incremental discounted cost-utility for monotherapy (sub-group analysis – baseline viral load and genotype)

No active treatment compared to PEG monotherapy (48 wks) high viral load + genotype 1					
No tx	£2,054,290	21,464	-	-	-
Mono tx PEG	£9,686,490	21,713	£7,632,200	249	£30,701
IFN monotherapy (48 weeks) compared to PEG monotherapy (48 wks) in high viral load + genotype 1					
Mono tx IFN	£4,365,204	21,535	-	-	-
Mono tx PEG	£9,686,490	21,713	£5,321,285	178	£29,963
No active treatment compared to PEG monotherapy (48 wks) high viral load + genotypes 2/3					
No tx	£2,054,290	21,464	-	-	-
Mono tx PEG	£8,988,031	22,920	£6,933,741	1,456	£4,761
IFN monotherapy (48 weeks) compared to PEG monotherapy (48 wks) high viral load + genotypes 2/3					
Mono tx IFN	£3,892,718	22,352			
Mono tx PEG	£8,988,031	22,920	£5,095,314	568	£8,966
No active treatment compared to PEG monotherapy (48 wks) low viral load + genotype 1					
No tx	£2,054,290	21,464	-	-	-
Mono tx PEG	£9,131,831	22,672	£7,077,541	1,208	£5,861
IFN monotherapy (48 weeks) compared to PEG monotherapy (48 wks) low viral load + genotype 1					
Mono tx IFN	£3,974,889	22,210	-	-	-
Mono tx PEG	£9,131,831	22,672	£5,156,942	462	£11,168
No active treatment compared to PEG monotherapy (48 wks) low viral load + genotypes 2/3					
No tx	£2,054,290	21,464	-	-	-
Mono tx PEG	£8,433,373	23,879	£6,379,083	2,415	£2,641
IFN monotherapy (48 weeks) compared to PEG monotherapy (48 wks) low viral load + genotype 2/3					
Mono tx IFN	£3,666,746	22,743	-	-	-
Mono tx PEG	£8,433,373	23,879	£4,766,627	1,137	£4,194

All SVRs from Lindsay *et al*.

Again, a sensitivity analysis was performed to examine the extent to which the cost-utility estimates for monotherapy differ according to variations in costs and assumptions. Table 35 shows estimates generated by varying the SVR according to the 95% Confidence Interval around the pooled estimate in our meta-analysis. The highest incremental cost per QALY, £14,692 was for the lower PEG SVR and higher IFN SVR (i.e. the smallest difference between groups). In contrast, the lowest estimate, £6,363 was for the higher PEG SVR and lower IFN SVR (i.e. the largest difference between the two treatments). This was the same pattern observed for dual therapy.

Table 29 Sensitivity analysis – variations in SVR (monotherapy)

Cost-utility estimates according to varying SVR, IFN monotherapy compared to PEG monotherapy			
		IFN SVR	
		12%	**17%**
PEG SVR	**27%**	£9,602	£14,692

	34%	£6,363	£8,404

Table 36 shows differences in cost-utility estimates according to variations in the discount rate. Predictably, estimates are lower at the 0% rate.

Table 30 Sensitivity analysis – variations in discount rate (monotherapy)

Range of incremental cost-utility ratio, varying discount rate from 0 to 6%. (costs/benefits)				
	0/0%	**3.5/3.5%**	**6/1.5%**	**6/6%**
No tx to mono PEG	£4,468	£8,590	£6,484	£12,463
Mono IFN to mono PEG	£5,952	£11,215	£8,404	£16,155

Table 37 illustrates how the estimates vary according to variations in drug costs. Again, the lowest estimates correspond to the lower drug cost variation.

Table 31 Sensitivity analysis – variations in drug costs (dual therapy)

Range of incremental cost-utility ratio, varying drug costs ±50%		
Drug cost	**minus 50%**	**plus 50%**
No tx to mono PEG	£2,953	£10,015
Mono IFN to mono PEG	£1,965	£14,843

4.2.4 Comparison of economic models

The design and results of the economic model in the current report were compared with those used by the manufacturers in their submissions to the NICE. The Roche submission includes an integral cost-effectiveness analyses, whilst the Schering-Plough submission cites data presented in a number of conference abstracts (some of which are described in the current report, see section 4.1.1) published by authors including Wong *et al.*, Stein *et al.*, and Siebert *et al*.

All three analyses used Markov models to estimate future clinical benefits and economic costs, expressed in terms of cost-utility analyses. Each model predicted progression to a number of disease states associated with hepatitis C over time, with a 30 year horizon in the current report and a 50 year horizon in the Roche model. The Schering-Plough model followed their cohort until all patients had died from liver-related or other causes.

- Utility estimates and transition probabilities in all three models are taken from the published literature, which, at present, is a fairly limited pool of data. Thus the three models model do not differ from each other greatly in this respect.
- Cost data –
    - The Roche version of ribavirin ('Co-Pegus') was used in all estimates in their model with drug costs taken from MIMMS (February 2003). For genotype 2/3 patients Roche

ribavirin was dosed at 800mg per day (based on an unpublished trial by Hadziyannis *et al*. the detailed data of which are commercial in confidence) in contrast to the SHTAC model where the drug is dosed at 1,200 per day (except for the 'additional analyses based on unpublished data' which doses the drug at 800mg in some comparisons). Use of a quantitative PCR test at £12 weeks was considered a relatively small proportion of the lifetime total costs and so is not modelled in the base case analysis. An expert panel of UK hepatologists estimated resource utilisation in the respective health states. Standardised unit cost estimates are estimated by the Pharmaceutical information cost assessment system.
    - The Schering-Plough submission is rather less detailed about costs sources, but does refer to conference abstracts containing a little more detail on drug costs[146;147].
    - All three models employed the same discount rate, with costs discounted at 6% and benefits at 1.5%.
- Treatment duration –
    - Roche: Genotype 2/3 patients were only treated for 24 weeks. 19% of genotype 1 patients who had not responded by 12 weeks were removed from the model and PCR testing was not conducted on genotype 2 and 3 patients at 12 weeks as only a minority had not responded at this time. PCR testing occurs at week 24 for non-pegylated interferon, with a drop out rate of 43%. An additional 4% of PEG treated patients were removed at 24 weeks.
    - Schering-Plough: Genotypes 2/3 patients were also only treated for 24 weeks, whilst genotype 1 patients were treated for 48 weeks with application of a 12 week stopping rule with treatment only continued for those negative at that time (with further re-evaluation at 24 weeks). The monotherapy analyses assumed a full 48 week treatment regimen for all patients (ITT analysis).
    - In the current report the primary cost per QALY estimates are based on all patients being treated for a full 48 weeks (intention to treat analysis, ITT). Separate cost per QALY estimates were produced to examine the effect of removing genotype 1 patients at 12 weeks (19% removed from the model), and for treating genotype 2/3 patients for only 24 weeks.
- In summary, the three models are broadly comparable in terms of design, assumptions and inputs. The model in the current report differs in that it has a shorter time horizon (30 years instead of the 50 years used by Roche); with treatment duration used in the main cost-utility analyses based on the all patients treated for 48 weeks without removal of patients at 12 or 24 weeks (i.e. ITT analysis). Efficacy data (i.e. SVR) were taken as much as possible from fully published RCTs, in contrast to unpublished conference abstract data.

Table 38 presents a comparison of both PEG dual therapy and PEG monotherapy against no active treatment, whilst Table 39 presents a comparison of both PEG dual therapy and PEG monotherapy against IFN dual therapy and IFN monotherapy, respectively. In general the cost-utility estimates reported by the drug manufacturers were lower than those from our model, and Roche's estimates were lower than Schering-Plough's. The higher estimates in our base case analysis may be due to the fact that, as stated above, patients were not removed from the model at 12 or 24 weeks, thus drug costs, one of the main drivers influencing the cost per QALY, are higher. Our shorter time horizon may also be influential, with less time for long-term benefits to manifest themselves.

Table 32 Incremental cost-utility for PEG dual therapy / PEG monotherapy compared to no active treatment

	SHTAC		**Roche**		**Schering-Plough**	
	dual tx	mono tx	dual tx	mono tx	dual tx	mono tx
All patients	£6,045	£6,484	-	-	£1,700	£4,600
Genotype 1	£7,340	£15,060	-	-	£2,500	£8,800
Genotypes 2/3	£4,216	£3,890	-	-	£670	£2,100

SHTAC - Southampton Health Technology Assessment Centre (i.e. the authors of the current report)

Table 33 Incremental cost-utility: PEG dual therapy / PEG monotherapy compared to IFN dual therapy / IFN monotherapy

	SHTAC		**Roche**		**Schering-Plough**	
	dual tx	mono tx	dual tx	mono tx	dual tx	mono tx
All patients	£12,123	£8,404	£914	£995	£3, 900	£6, 000
Genotype 1	£10,848	£18,510	£5, 591	£749	£3, 600	£11, 400
Genotypes 2/3	£7,051 - £37,578*	£6,693	-£2, 204	£ 1,266	£5, 400	£3, 200

*lower estimate based on SVR from Fried *et al,* higher estimated based on SVR from Manns *et al.*

4.2.5. The economics of treating mild disease.

As discussed in section 3.6, there is currently uncertainty about whether to treat patients with mild disease. The results of the UK Trial are due out in the autumn of 2003. But we have some data from other studies at present, and can speculate as follows.

The benefits of treating those with mild disease would be;

1. improvement in quality of life. The average QoL of people with chronic HCV infection is reported to be 0.95. If we assumed that an SVR was sustained for 20 years (i.e. a conservative estimate based on the lifetime of the patients), then successful treatment would give 1.0 QALYs (0.5 x 20). This ignores any short-term diminution of quality of life due to side-effects while on treatment.
2. reductions in future serious liver disease. This would be less in those with mild disease since progression is slower, but 33% do progress over a few years, and some will go to develop serious disease.
3. reductions in transmission of virus.

In the absence of hard data on items 2 and 3, we can consider what the cost-effectiveness of treatment would be if the only gain was improved quality of life in responders. If 100 patients were treated, and 55% had a SVR, the QALY gain over 20 years would be 55 QALYs (NB. this would need to be discounted). The cost of treating 100 patients for 24 weeks would be around £900,000 and for 48 weeks would be around £1,700,000, which might give (undiscounted) costs per QALY of around £16,000 and £31,000 respectively. Since there would undoubtedly be some future serious liver pathology prevented in those who would have progressed, hence off-setting treatments cost by future savings (even after discounting), the true cost per QALY will be less.

However, there are various uncertainties around all these costs. The response rate in milds in the Swedish trial[114] was 54% on combination therapy, but that was with non-pegylated interferon. Results would be expected to be better with pegylated. That trial gave treatment for 53 weeks in responders, and it might be that 24 weeks would suffice. Various stopping rules could be applied to reduce costs, by earlier discontinuation in non-responders.

The relatively low costs per QALY obtained when taking the improvement in quality of life as the only benefit arise because the cost of treatment is short-term (24 weeks or 48 weeks) but the benefit in those who respond is for life.

The financial implication for the NHS would be large, because there are many people with mild disease, and it is assumed that they are currently not treated.

Further consideration of the economics of treating this group will need to await the results of the UK trial, funded by the HTA programme.

5. Implications for other parties

5.1 Acceptance of assessment and treatment

One implication of the variations in prevalence is that the cost of therapy may vary enormously between health authorities. Some, particularly in the

cities or districts with large numbers of injecting drug users[e], might have a much higher total cost than others, although economies of scale may be achieved through treating sufficient quantities of patients. However, this assumes high compliance with treatment. We have good data on acceptance rates of initial assessment (which currently has to include liver biopsy, since clinical and biochemical assessment is not a good guide to severity of liver damage in the early stages) [11;26]. Data from the clinical trials of pegylated interferon indicate that adverse events were certainly no worse with this treatment than with non-pegylated interferon. Patients also report higher quality of life with pegylated interferon during treatment than non-pegylated, suggesting better rates of compliance.

However, advice from clinical colleagues is that compliance by injecting drug users is poor, particularly as treatment is appropriate only for those who cease injection (because of high risk of re-infection otherwise). This may counter the point made above, since non-compliance would make provision of treatment more affordable. The specific needs of this client group need to be assessed with services adapted accordingly.

5.2 Implications for others

One possible effect of provision of an assessment and treatment package for hepatitis C is that it might reduce the spread of infection by persuading injecting drug users to stop injecting. This is speculative and at present is unproven.

5.3 Provision of care

There would probably be merit in providing care through a limited number of specialist clinics, partly because of the nature of assessment and treatment, and partly to facilitate systematic data collection, including long term follow-up. This would also foster further research into response rates and prediction factors, which by allowing better targeting of treatment, would improve cost-effectiveness and reduce costs.

6. Factors relevant to NHS

The prevalence of hepatitis C is uncertain, 200,000 – 400,000 in the U.K, and it is likely that many infected people are unaware of their disease. As many as 15 - 35 % will clear virus spontaneously within 2 – 6 months. The availability of effective treatment will influence the active search and screening for infected patients in the population as will the increased costs of treatment. With this background the budget impact of pegylated interferon compared to non-pegylated interferon treatment can only be speculative. Roche point at a cost of £13m per annum and Schering-Plough at about £50m. In the long term some costs would be offset by less secondary complications.

[e] To be eligible for treatment they would have to have ceased using injected drugs.

As previously mentioned, the cost of therapy for HCV will not fall evenly on all areas of the country, because of differences in prevalence of IDU, although the key group in this case is former drug users. Another factor to take into account is that there will be a large group of people infected with hepatitis C over many years; once they have all been treated (if diagnosed) costs would fall.

It is not possible to predict whether other and perhaps more effective drug combinations will appear (see section 7.2 for future research needs). Some have argued that those with only mild disease could wait in the hope of better treatments in future ***(Academic in confidence information on progression in patients with mild disease has been removed).***

The fact that pegylated interferon treatment appears clinically-effective and cost-effective will augment the Hepatitis C Strategy for England[143] which places emphasis upon effective anti-viral treatment as described in the existing NICE guidance, which will be updated by the forthcoming guidance. Treatment forms part of a wider strategy to ensure effective monitoring, prevention, diagnosis and care for those infected, in terms of managed clinical networks and co-ordinated pathways of patient care.

7. Discussion

7.1 Assumptions, limitations and uncertainties

The nature of the model makes results sensitive to the assumptions used. The costs gathered from NHS registers or from other verifiable sources stem from a relatively short period of time during which pegylated interferon has been available. On the other hand, treating or not treating hepatitis C will, in many cases, have consequences for 30 years or more. Small changes in elements of the model will therefore have large long-term consequences, as the sensitivity analyses clearly show.

It should be noted that the clinical-effectiveness data that are used in the cost-utility model come from relatively few trials. Therefore, some effectiveness estimates may be based on relatively small numbers of patients. This is particularly true when considering subgroups of patients with different combinations of viral genotype and baseline viral load, for instance. In addition, although some trials stratified their randomisation on the basis of these baseline characteristics, other results are based on post hoc subgroups. Finally, some data have been drawn from trials that have not yet been fully published. The methods in these trials cannot be adequately scrutinised and therefore should be considered with some caution.

Apart from uncertainties in data the model also has to work in a simplified manner so that relations between the data elements need to be linear or at best loglinear (i.e. percentage changes). For instance, we lack natural history data to model more complex relations such as disease progression over a long-term period.

As was noted in section 3.2.1 there is a relatively high withdrawal rate from treatment even in the context of a trial. These withdrawals are for several reasons, but include patients who simply failed to comply with the fairly rigorous treatment regimen. It has been shown that patients with higher rates of compliance are associated with higher SVRs within the context of clinical trials, particularly for genotype 1 patients (see section 3.2.2). The rate of compliance and treatment withdrawals in practice may be even higher than seen in the trials. Ways to maximise compliance and adherence in this population, many of whom are injecting drug users and have psych-social difficulties, need to be considered. This is particularly important issue for those former IDU's who are at risk of resuming their drug use, thus dropping out of treatment. Specialist centres may achieve better compliance through the use of specific reminder systems and other management methods.

7.2 Further research needs

Pegylated interferon is a relatively new intervention in the treatment of hepatitis C and therefore there are a number of gaps in the evidence where further research is needed:

- There are no trials in which the efficacies of therapy with PEG α-2a and PEG α-2b are directly compared. It would be useful to compare the efficacy of these two pegylated interferons with and without ribavirin to determine if there are any differences either in efficacy or in adverse events. One area where the two drugs differed in the current report was the difference in SVRs for patients infected with genotypes 2 and 3. In the dual therapy trial of PEG 2a there was little difference between PEG and IFN treated patients, whilst in the other dual therapy trial (PEG 2b) the difference was greater, leading to widely different cost-utility estimates. This was probably a chance event in the Manns *et al*. trial, where the results of dual therapy with non-pegylated interferon were better than expected.
- As there are many patients who have been treated with previous therapies (non-pegylated interferon with or without ribavirin) without achieving a sustained response, there are patients who still need treatment that may clear their virus. There are no full reports of re-treatment of previous non-responders using pegylated interferon (either with or without ribavirin).
- There is very little information on the efficacy of treatments for hepatitis C (particularly using PEG) in patients who have other co-morbidities. With increased life-expectancy in patients with HIV, the effects of hepatitis C on morbidity and mortality in this population have become more salient. Trials testing regimens

including PEG should be conducted in this population (and some are ongoing, see Appendix 11). Many patients with haemophilia or renal disease are infected with hepatitis C and little information is available about the efficacy of hepatitis treatments in these populations. Generally, patients with co-morbidities have been explicitly excluded from the primary efficacy trials for PEG. Careful evaluation of adverse events may be particularly important in these patient groups with co-morbidities because of the possibility of adverse interactions of hepatitis C treatment with other drugs that these patients may be taking. Others (e.g. IDUs) may be at higher risk of certain adverse events such as psychiatric events such as severe depression.

- Despite increases in efficacy with the use of PEG over IFN, many patients remain infected with hepatitis C. Other treatment regimens that may prove to be overall more effective than dual therapy with PEG should be evaluated. For instance, treatment regimens that include amantadine may merit further evaluation. At least one conference abstract was identified in this review whereby patients were treated with triple therapy (PEG + RBV + AMA).
- There is some evidence that treatments for the eradication of hepatitis C may improve liver histology even in patients who do not clear the virus. More evidence about the long-term outcomes for such patients would be useful. In addition it would be useful to prospectively test which treatment regimens achieve the best improvements in liver histology and which are most cost-effective.
- In the context of existing trials of PEG that generally treated patients for 48 weeks, secondary analyses have suggested that stopping treatment relatively early (e.g., 12 weeks for patients with non-1 genotypes or 24 weeks for patients with genotype 1) may be a cost-effective approach to treatment that would also reduce the exposure of patients unlikely to benefit to adverse events. Prospective tests of these stopping rules would be useful, particularly with concurrent collection of cost data.
- As mentioned in section 3.6, an HTA Programme funded RCT (with concurrent collection of cost data in some centres) is due to report in mid to late 2003 on the effects of treatment for hepatitis C in patients with mild disease. Evaluation of results from such trials will be important to determine whether such treatment is effective and cost-effective. Treating patients with mild disease would dramatically increase the potential population for hepatitis C treatment.
- Further investigation of treating patients with acute hepatitis C may be merited in order to potentially avoid the long-term morbidity involved for some patients when they reach the stage of chronic infection. However, careful attention to treatment of patients who are acutely symptomatic versus those who are infected but remain asymptomatic may be important in terms of treatment efficacy, the overall populations to be treated, and in the potential cost-effectiveness of treating patients with acute infection.
- Problems that may occur in a minority of patients with Hep C such as cryoglobulinaemia and vasculitis are not likely to be the subject

of clinical trials because of the relatively small number of patients affected. However, clinicians point out that in some patients with vasculitis due to viral/antibody complexes the vasculitis can resolve after long term treatment. Appropriate treatment of such patients needs to be addressed.

- Additional psychological effects on quality of life due to Hep C need to be evaluated. For instance, the simple fact of being infected with a transmissible disease is a significant motivator for treatment for many patients.
- Further research is needed on the treatment of children and adolescents with Hep C. Previous studies of interferon monotherapy in children have been generally small, uncontrolled trials involving highly selected patients. New therapies, including PEG, should also be studied in children. The long-term safety of these medications also needs to be studied in children.

7.3 Should patients with mild disease be treated?

An interim position is needed while we wait for the results of the UK Mild HCV study. The case for treatment depends at present on the unpublished Trent data on progression, and the quality of life reduction in untreated patients with hepatitis C. If the average reduction is 0.05 QALY, and if an SVR indicates permanent clearance, then given the fairly young age of many people with hepatitis C, successful treatment will achieve at least 20 years of gain, equating to 1.0 QALY. Hence it could be argued that there is a case for treating mild disease on QoL gains alone.

8. Conclusions

Pegylated interferon is more clinically effective than non-pegylated interferon both as dual therapy, and as monotherapy for those unable to tolerate ribavirin. It is also relatively cost-effective, particularly for patients with genotypes 2 and 3. There is some evidence to suggest that a proportion of patients with genotype 1 who do not respond by week 12 can be removed from treatment, as it is unlikely that they will experience a later, sustained response. This will lead to some cost-savings (mainly in terms of drug costs), and will spare patients the adverse effects that are associated with treatment (which appear to be no worse than those experienced with non-pegylated interferon). Evidence for the clinical and cost-effectiveness of antiviral treatment in patients with mild disease (i.e. non-pegylated and ribavirin dual therapy) is imminent. If it can be assumed that treatment is effective and has benefits for patients' health related quality of life this would be an argument for extending treatment to a much larger group of patients than who are currently eligible.

9. Appendices

Appendix 1 Chronic hepatitis C – natural history

Introduction

The natural history of hepatitis C is still poorly understood. Information on the long term outcomes for untreated patients is required for a number of reasons, including to provide a baseline for estimating the relative cost-effectiveness of the various treatment options. There are several problems associated with assessing natural history.

- The first is that it is a relatively new disease, in the sense that the virus was identified only in 1989. However since it seems to have been responsible for about 95% of cases of what was called "non-A, non-B" hepatitis that can be used as a reasonably accurate proxy.

- The second is that because most people have no acute illness at onset, the date of onset and hence the duration of disease is often uncertain. However there have been a number of unfortunate events involving contamination of blood or blood products which have led to several outbreaks with a point source, allowing accurate analysis by duration.

- This leads to a third issue – is it safe to extrapolate from the populations involved in these outbreaks, to the different patient mix of those who have been infected more recently?

For the purposes of this review, we need to make a number of assumptions for economic modelling, to do with progression from one disease stage to another, both in terms of numbers who progress, and time taken to progress. The group which most concern us are those who develop the more serious consequences such as decompensated cirrhosis and hepato-cellular cancer, many of whom will die, partly because of the seriousness of these conditions to patients, partly because of the potential savings to the NHS if some of these conditions can be avoided. However the much lesser effect on quality of life in those with mild chronic hepatitis should also be borne in mind, since although the effect is much smaller, numbers are greater.

Review of studies

The natural history has been reviewed by Seeff (1997; 2002) [6;144]. He notes that the problems of assessing natural history include:

- the time of initial infection is often not known – in about 60-80% of patients.
- we need representative cohorts, in order to avoid the bias towards severity if only those referred with problems were used.

- the very long follow-up time needed, because some consequences take decades to appear.
- the difficulty in obtaining natural history for recent patients, because of treatment with anti-viral therapy (Although a proportion do not respond, the responders may be a group who would have had a better natural history).
- the need for population control groups (particularly if assessing symptoms such as tiredness).

Infection from contaminated blood.

1. Anti-rhesus immunisation
   In Ireland in 1977, a batch of anti-D immunoglobulin was contaminated with the hepatitis C virus. Crowe *et al*. (1995) [145] and Power *et al*. (1994) [146] followed up 232 women 17 years after inoculation. 70% had no symptoms, and the main symptom in the rest was fatigue. Liver biopsy showed mild or mild/moderate inflammation in 70%, moderate in 24% and severe in 7%. Only 2.4% had cirrhosis, mostly early (i.e. nodules with bridging fibrosis). This would be considered a low risk group because of their age.

2. Clotting factors for haemophilia.
   Darby *et al*. (1997) [147] studied mortality in men who received clotting factor after the introduction of large pool methods (which replaced treatment by blood transfusion, starting in 1969, and which greatly increased the risk of infection). The risk of infection with hepatitis C is close to 100% in this group, dropping to 60% in those who received cryoprecipitate. Darby and colleagues used the National Haemophilia Register to create a cohort of men who were treated from 1969 to 1985, and then obtained data on deaths from liver disease or liver cancer, in order to estimate interval between infection and death. There was a 17-fold risk of death from liver disease, after excluding those with HIV infection. The risk was not apparent for the first 10-15 years of follow-up, but became noticeable after 20 years. There was a strong relationship with age, with cumulative risks of liver-related disease including cancer at 25 years being 14% in those with severe haemophilia who were over 45 years of age at first known exposure, compared to 2% in those aged 25-44 at infection.

3. Blood transfusion
   Seeff (1997) [144] summarises the findings of 5 studies of transfusion-associated HCV infection (Hopf et al 1990; Di Bisceglie et al 1991; Tremolada et al 1992; Koretz et al 1993; Mattson et al 1993). There was a range of follow-up intervals of 8 to 14 years. Cirrhosis had developed in 8 to 24%; liver cancer was rare; liver-related deaths ranged from 2 to 6%. Most patients had no symptoms. In another two studies where subsets of patients believed to have been infected by transfusion could be identified, the mean durations between transfusion and development of cirrhosis and HCC were 10 and 14 years, and 29

and 28 years, in the studies by Kiyosawa et al (1990) and Tong et al (1995) respectively.

(In a paper on current practice, Regan *et al*. (2000) [148] followed up 5579 recipients of 21,923 units of blood, and found that screening now ensures prevention of hepatitis C by blood transfusion. There was not a single instance of transmission.)

In the UK, the National HCV Register provides a valuable resource for natural history and other studies (Harris *et al.* 2002) [149]. It is based on the national "lookback" exercise carried out in 1995, of all patients who received blood transfusions from donors found when testing started in 1991 to be HCV positive. The study reports on 924 patients with known date of infection traced during the HCV lookback programme and 475 transfusion recipients who tested negative for antibodies to HCV (controls). This study reports on the results for the first 10 years since infection. As of 1999, 117 of 924 eligible patients had died. All cause mortality was not significantly different between patients and controls (Cox's hazards ratio 1.41, 95% CI 0.95 – 2.08). Patients were almost six times more likely to die directly from liver disease, but this difference was not significant. (The excess of liver related deaths among the patients may be partially explained by the fact that knowledge of HCV status may influence the content of the death certificate.) Forty percent of those who died from liver disease were known to have consumed excess alcohol. The majority of infected patients had no signs or symptoms of liver disease, but nearly 40% had abnormal liver function and 91% of patients biopsied had abnormal liver histology. Patients who had developed symptoms were more likely to have been infected for longer, to be positive for HCV-RNA, and to have acquired the infection at an older age. Those with features of severe liver disease were also more likely to be male. This study suggests that HCV infection does not have a great impact on all cause mortality in the first decade of infection, but infected patients have an increased risk of dying from a liver related cause, particularly if they consume excess alcohol. Continued evaluation of this cohort will provide more information about the outcome of HCV infection over a longer time course.

Studies in blood donors.

Since the start of testing for HCV in blood donors, many asymptomatic cases of hepatitis C have been found. Alter *et al*. (1997) [150] studied a group of 481 blood donors who had anti-HCV antibodies. 86% had HCV RNA indicating chronic infection; the other 14% had presumably recovered spontaneously. Most of those with chronic hepatitis C had only mild liver disease. In 74 subjects, a reasonable estimate of time of onset of infection could be made, either because transfusion was the only apparent risk factor, or because IV drug use had been carried out for a limited period. Data from these patients suggest an interval to severe hepatitis of 14 years, and to cirrhosis of 27 years. Those with severe outcomes (15% in the NIH

study) tended to be older (most over 60 at onset of infection) and a high proportion had a history of alcohol abuse.
In this study, the likely sources of infection were blood transfusion, intranasal cocaine use, IV drug use, ear piercing in males, tattooing.

Progression to cirrhosis

Seeff (2002)[6] in his review of natural history studies notes the discordance in mean frequency in evolution to cirrhosis according to study design. The mean frequency was 42% for retrospective studies, 11% for prospective studies and 2.1% for retrospective-prospective cohort studies. Lowest rates of progression were among young people, particularly young women. The higher estimation from retrospective studies was probably because they included patients with established disease sampled from the referral base, prospective studies from people infected via blood transfusions, with the retrospective-prospective studies benefiting from including a wide variety of ages, sexes, from acute infection to long term follow-up.

Freeman(2001) [151](as cited in Seeff) [6]conducted a systematic review of studies specifically to investigate progression to cirrhosis. Four categories of studies were identified, and rates of cirrhosis after 20 years were estimated for each:

- Cross sectional studies of patients referred to tertiary care centers (n= 33 studies, rate= 22%, (95%CI, 18-26%), with a mean age of 29 years at acquisition of infection
- Longitudinal post-transfusion hepatitis studies (n=5 studies), rate =24%, (95% CI, 11-37%), with a mean age of 42 years at acquisition of infection
- Cross-sectional surveys of persons newly diagnosed at blood donor screening (n=10 studies), rate = 4% (95%CI, 1-7%), with a mean age of 22 years at acquisition of infection
- Longitudinal community-based studies (n=9 studies), rate = 7% , (95%CI, 4-10%), with a mean age of 26 years at acquisition of infection.

The authors of this study suggested that the community-based cohort studies with a mean frequency of 7% for the development of cirrhosis were the most representative for the estimation of progression in the general population. They identified older age at infection, sex, and heavy alcohol intake as the major factors associated with rapid disease progression.

Cohorts of patients with chronic hepatitis C.

Poynard *et al.* (1997) [4] studied a French cohort of 2235 patients with liver biopsies, though not all had known the date of onset. Estimated duration of infection to cirrhosis was 30 years, ranging from 13 years in men infected over the age of 40, to 42 years in women who were infected under the age of 40 and who did not drink alcohol. The main risk factors for more rapid progression were age, alcohol consumption and male sex. This study is useful for the mix of sources of infection – transfusion 39%, IV drug use

25%. There seemed to be no relationship between source of infection and risk of progression, which implies that we need have less concern about the generalisability of findings from those groups with known date of infection.

More recently, Poynard *et al*. (2001) [8] reported results of another cross-sectional cohort study of 2313 untreated patients infected either through IV drug use, or blood transfusion and who underwent a single biopsy. The aim was to assess disease progression in terms of the linearity or other configuration of fibrosis progression. Progression was modelled using the Hazard Function (the probability an individual experiences the event of interest, such as fibrosis progression, during a small time interval, given that the individual has survived up to the beginning of the interval). There were approximately four periods with a linear progression:

- during the first 10 years of infection there was little progression (except for patients infected after the age of 50),
- for the next period of 15 years progression was slow and regular,
- progression was intermediate during the next 10 years,
- finally, during the final five years progression was at its fastest.

Regression analysis was performed to identify risk factors associated with fibrosis progression:

- Whatever the fibrosis stage there were higher probabilities of progression according to age at infection, with most rapid progression in patients infected after the age of 50.
- Alcohol consumption only affected progression for fibrosis stages F2, F3 and F4, after 10 years of infection.
- Male gender was associated with fibrosis independent of age at infection and of alcohol consumption, primarily for latter stages of progression.
- There was no significant relationship between genotype or viral load and progression.

Fattovich *et al*. (1997) [152] from the EUROHEP study (in which St Mary's in London was one of the 7 centres) followed 384 patients who already had compensated cirrhosis for a mean of 5 years. The 5-year risk of decompensation was 18%, and of hepatocellular cancer 7%. The 5-year survival was 91% in all patients, but 50% in those who developed decompensated cirrhosis.

Di Bisceglie (1997) [153] reviewed the evidence on the development of hepatocellular cancer, and concluded that there was an incubation period of 2-3 decades between infection and HCC, and that it usually followed cirrhosis rather than developing de novo. Since about 20% of patients with chronic hepatitis C develop cirrhosis over the first 10 years, this suggests that between 2 and 7% will develop cancer by 20 years after infection. The risk is increased by alcohol and by concomitant infection with hepatitis B.

Are all patients at risk?

One issue which has yet to be resolved is whether all patients would develop cirrhosis if given sufficient time – i.e. that all progress but at different rates – or whether some would not progress beyond mild disease. Dienstag (1997) [154] believes that progression is inevitable, but that in some patients it might take up to 5 decades, with 20% developing end-stage liver disease at some time. Hoofnagle (1997) [155] notes that 20-30% of patients develop cirrhosis after a slow and insidious process, but comments that it is unclear whether the remaining patients would develop cirrhosis eventually, or not at all.

What is clear is that current methods of assessing risk are not good enough to identify sub-groups of patients who are not at risk, and the implication of that is that all need to be treated.

Conclusion

There are still uncertainties about the natural history, but it appears that;

- most (85%) patients who are infected develop chronic hepatitis C
- most are asymptomatic; progression is usually very slow and insidious
- some groups – older patients; men; alcohol users – are at higher risk of progression
- source of infection does not affect risk of progression once factors such as age are taken into account, and so the natural history observed from the groups infected via blood transfusion and products can be applied to newer cohorts such as IDUs
- 20% will develop cirrhosis by 20 years duration
- about 2.5% of those with cirrhosis will develop hepatocellular cancer per annum
- once decompensated cirrhosis or cancer develop, most die within a year (if not given a liver transplant).

Appendix 2 Search Strategy – Pegylated interferon alpha in chronic hepatitis C:
Searched from 2000 to present March 2003

Databases	**Search strategy**
Cochrane Library	Peg* OR polyethylene Glycol and interferon* Hepatitis-C or HCV and #1
Medline	Search hist: hepc_medsrch ((((('Interferon-Alfa-2b' / all subheadings in MIME,MJME) or ('Interferon-Type-I' / all subheadings in MIME,MJME) or ('Interferon-Alfa-2a' / all subheadings in MIME,MJME) or ('Interferon-Alfa-2c' / all subheadings in MIME,MJME) or ('Interferon-Type-I-Recombinant' / all subheadings in MIME,MJME) or ('Interferon-alpha' / all subheadings in MIME,MJME) or (interferon alpha in ti,ab) or (interferon alfa in ti,ab) or (interferon*) or (Roferon-A or Viraferon)) and ((peginterferon) or (pegylat* near interferon) or (peg* or polyethylene glycol) or (ViraferonPeg or Pegasys))) and ((hepatitis-c or HCV) or (('Hepatitis-C' / all subheadings in MIME,MJME) or ('Hepatitis-C-Chronic' / all subheadings in MIME,MJME)) or ('Hepacivirus-' / all subheadings in MIME,MJME))) or (((((('Interferon-Alfa-2b' / all subheadings in

	MIME,MJME) or ('Interferon-Type-I' / all subheadings in MIME,MJME) or ('Interferon-Alfa-2a' / all subheadings in MIME,MJME) or ('Interferon-Alfa-2c' / all subheadings in MIME,MJME) or ('Interferon-Type-I-Recombinant' / all subheadings in MIME,MJME) or ('Interferon-alpha' / all subheadings in MIME,MJME) or (interferon alpha in ti,ab) or (interferon alfa in ti,ab) or (interferon*) or (Roferon-A or Viraferon)) and ((peginterferon) or (pegylat* near interferon) or (peg* or polyethylene glycol) or (ViraferonPeg or Pegasys))) and ((ribav?rin) or ('Ribavirin-' / all subheadings in MIME,MJME) or (rebetol))) and ((hepatitis-c or HCV) or (('Hepatitis-C' / all subheadings in MIME,MJME) or ('Hepatitis-C-Chronic' / all subheadings in MIME,MJME)) or ('Hepacivirus-' / all subheadings in MIME,MJME))) or ((((((('Interferon-Alfa-2b' / all subheadings in MIME,MJME) or ('Interferon-Type-I' / all subheadings in MIME,MJME) or ('Interferon-Alfa-2a' / all subheadings in MIME,MJME) or ('Interferon-Alfa-2c' / all subheadings in MIME,MJME) or ('Interferon-Type-I-Recombinant' / all subheadings in MIME,MJME) or ('Interferon-alpha' / all subheadings in MIME,MJME) or (interferon alpha in ti,ab) or (interferon alfa in ti,ab) or (interferon*) or (Roferon-A or Viraferon)) and ((peginterferon) or (pegylat* near interferon) or (peg* or polyethylene glycol) or (ViraferonPeg or Pegasys))) and ((ribav?rin) or ('Ribavirin-' / all subheadings in MIME,MJME) or (rebetol))) and ((amantadine or amantadine hydrochloride or Lysovia) or ('Amantadine-' / all subheadings in MIME,MJME))) and ((hepatitis-c or HCV) or (('Hepatitis-C' / all subheadings in MIME,MJME) or ('Hepatitis-C-Chronic' / all subheadings in MIME,MJME)) or ('Hepacivirus-' / all subheadings in MIME,MJME))) IFNa + Amantadine + HepC
Embase	Search strategy: emb_hepc_RCTs (((explode 'interferon-' / all subheadings) or (interferon*)) and ((peg* or polyethylene glycol) or (pegylat* near interferon) or (peginterferon) or (ViraferonPeg or Pegasys or Pegintron))) and ((hepatitis-c or HCV) or (('chronic-hepatitis' / all subheadings) or ('hepatitis-C' / all subheadings) or ('Hepatitis-C-virus' / all subheadings))) Interferon + amantadine + hepC (for comparatives)
PubMed (for recent studies)	Peg* and interferon*
Web of Science Proceedings	hepatitis-c and (peg* and interferon)
Science Citation Index (SCI)	hepatitis-c and (peg* and interferon) hepatitis-c and amantadine
National Research Register (NRR)	Peg* OR polyethylene Glycol and interferon* and hepatitis-c
Edina BIOSIS	Peg* and interferon*
CRD HTA	Peg* and interferon*
NHS EED	Hepatitis-c and interferon* (no pegylated interferon costs)

Appendix 3 Inclusion worksheet for primary clinical-effectiveness trials

Trial Name or Number:				
Patients with **chronic Hepatitis C**? (treatment naïve, relapsed, or not responded to previous treatment regardless of source of infection or severity)	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	Type:
Pegylated interferon treatment programme? *NB exclude interventions without pegylated interferon (unless in re-treatment of*	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	

previous non-responders)				
Design: RCT or sys review	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	
Appropriate **comparator**? 1) dual PEG v dual std 2) mono PEG v mono std 3) triple PEG v dual PEG In re-treatment: 1) dual PEG v mono std 2) triple PEG v mono std *NB exclude screening for Hepatitis C*	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	Note here if dual or triple std v mono std in retreated:
Report one or more of **primary outcomes**: sustained clearance of infection (absence of viral RNA 6 mo or longer after end of treatment); adverse effects; quality of life; long-term complications avoided	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	
Final Decision	**INCLUDE**	**UNCLEAR (Discuss)**	**EXCLUDE**	**Results of Discussion:**

Appendix 4 Conference abstracts of trials involving pegylated interferon in hepatitis C

Study	Interventions	Design & Reported Primary Outcome	Participants
Triple Therapies versus Dual Therapies			
Afdhal, *et al*, 2001[156]	1. PEG α-2a + RBV 2. PEG α-2a + mycophenylate mofetil 3. PEG α-2a + amantadine 4. PEG α-2a + amantadine + RBV	RCT Virological response 24 wk	n = 93 not responded to ≥ 12 wk IFN + RBV
Herrine, *et al,* 2001[157] SAME AS AFDHAL?	1. PEG α-2a + RBV 2. PEG α-2a + mycophenylate mofetil 3. PEG α-2a + amantadine 4. PEG α-2a + amantadine + RBV	RCT Virological response 12 wk	n = 90 broke through or relapsed on IFN α-2b + RBV
Di Bisceglie, *et al*, 2001[158]	1. PEG α-2a + mycophenylate 2. PEG α-2a + amantadine 3. PEG α-2a + mycophenylate + amantadine 4. IFN α-2b + RBV	RCT Virological response 24 wk	n = 153 previously untreated with CHC
Lawitz, *et al*, 2002[159]	1. PEG α-2b (1.5 mcg/kg/wk) + RBV (13 mg/kg/wk ± 2) + amantadine (100 mg bid) 2. PEG α-2b (1.5 mcg/kg/wk) + RBV (13 mg/kg/wk ± 2)	RCT Virological response	n = 1000 treatment naive
Dual PEG Therapy versus Dual IFN Therapy or Monotherapies			
Hassanein, *et al,* 2001[133]	1. PEG α-2a + RBV 2. PEG α-2a + placebo 3. IFN α-2a + RBV	RCT QoL (SF-36 and FSS)	n = not reported chronic Hep C
Zeuzem, *et al*, 2001[160]	1. PEG α-2a (180 µg qw) 2. PEG α-2a (180 µg qw) + RBV (1000 – 1200 qd) 3. IFN α-2a (3 MIU tiw) + RBV (1000 – 1200 qd)	RCT viral kinetics	n = 36
McHutchison, *et al*, 2001{607)	1. PEG α-2b (0.5 µg/kg/wk) + RBV 2. PEG α-2b (1.5 µg/kg/wk) +RBV 3. IFN α-2b + RBV	analysis of included RCT not reported in primary report[41] Effect of adherence on SVR	n = 1530 treatment naive
Lindsay, *et al*, 2000[161]	1. PEG α-2b (0.5 µg/kg or 1.0 µg/kg or 1.5 µg/kg 2. IFN α-2b (3 MIU TIW) + RBV (1000-1200 mg daily) 3. IFN α-2b (3 MIU TIW)	pooled data from 3 RCTs SVR in Caucasians, Blacks, and Hispanics	n = 2173 CHC, elevated ALT, compensated liver disease

Wong, *et al* 2001[162]	1. PEG α-2b (0.5 µg/kg/wk) + RBV 2. PEG α-2b (1.5 µg/kg/wk) +RBV 3. IFN α-2b + RBV	economic analysis of included RCT not reported in primary report[41]	n = 1530 treatment naive
Buti, *et al* 2002[163]	1. PEG α-2b (1.5 µg/kg/wk) +RBV (800 mg/day) 2. Peg α-2b + RBV (adjusted for body weight) 3. IFN α-2b + RBV	economic analysis (Spain) of effectiveness data from an included RCT [41]	n=1530 treatment naive
Siebert, *et al* 2002[164]	'PEG α-2b + RBV compared with IFN α-2b + RBV'	cost-effectiveness analysis (Markov model) of effectiveness data from an included RCT[41]. Analyses in euros/QALY	n = not stated (assume 1530) treatment naive
Monotherapies			
Shiffman, *et al*, 1999[165] SAME AS REDDY?	1. PEG α-2a (45, 90, 180, or 270 µg qw) 2. IFN α-2a (3 MIU tiw)	RCT SVR	n = 155
Neumann, *et al*, 2000[166]	1. PEG α-2a (180 µg qw) 2. IFN α-2a (6 MIU then 3 MIU)	analysis of included RCT not reported in primary report[53] Relation between rapid viral response and SVR	n = 513 IFN naïve
Pockros, *et al*, 2000[167]	1. PEG α-2a (180 µg qw) 2. IFN α-2a (3 MIU or 6 MIU then 3 MIU)	pooled data from 3 RCTs Relation of genotype and baseline histology with SVR	n = 1130 IFN naïve
Sherman, *et al,* 2000[168]	1. PEG α-2a qw (180 µg) 2. IFN α-2a tiw (3 MIU or 6 MIU then 3 MIU)	database from RCTs SVR	n = 1205 in database CHC, genotype 4 (n=16)
Shiffman, *et al*, 2000[169]	1. PEG α-2a qw (180 µg) 2. IFN α-2a tiw (3 MIU or 6 MIU then 3 MIU)	database from RCTs SVR	n = 1205 in database CHC, black (n=55)
Zeuzem, *et al,* 2000[170]	1. PEG α-2a (90, 135, or 180 µg qw) 2. IFN α-2a tiw (3 MIU or 6 MIU then 3 MIU)	pooled data from RCTs follow-up time for relapse following end-of-treatment response	n = 1441 IFN naive
Cooksley, *et al*, 2000[171]	1. PEG α-2a 2. IFN α-2a	RCT HRQL	n = 250 with cirrhosis
Kamal, *et al* 2001[172]	1. PEG α-2a 2. IFN α-2a (6MIU 12 wk then 3MIU 36 wk)	HCV specific CD4+ and cytokine responses	n = 28 previously untreated

Heathcote, *et al*, 2000[173]	1. PEG α-2a 2. IFN α-2a	pooled data from 2 RCTs Relation between SVR and histological response	n = 430 IFN naïve

Appendix 5 Quality Assessment Scale - experimental studies

Adapted from NHS Centre for Reviews and Dissemination (NHS CRD) Report 4

1. Was the assignment to the treatment groups really random?	
2. Was the treatment allocation concealed?	
3. Were the groups similar at baseline in terms of prognostic factors?	
4. Were the eligibility criteria specified?	
5. Were the point estimates and measure of variability presented for the primary outcome measure?	
6. Did the analyses include an intention to treat analysis?	
7. Were withdrawals and dropouts completely described?	

Some instructions for using a checklist for RCTs

Quality item	**Coding**	**Explanation**
1. Was the assignment to the treatment groups really random?		
Random sequence generation	**Adequate** **Partial** **Inadequate** **Unknown**	**Adequate**: random numbers table or computer and central office or coded packages **Partial**: (sealed) envelopes without further description or serially numbered opaque, sealed envelopes **Inadequate**: alternation, case record number, birth date, or similar procedures **Unknown**: just the term 'randomised' or 'randomly allocated' etc.
2. Was the treatment allocation concealed?		
Concealment of randomisation The person(s) who decide on eligibility should not be able to know or be able to predict with reasonable accuracy to which treatment group a patient will be allocated. In trials that use good placebos this should normally be the case, however different modes or timing of drug administration in combination with the use of small block sizes of known size may present opportunities for clinicians who are also involved in the inclusion procedure to make accurate guesses and selectively exclude eligible patients in the light of their most likely treatment allocation; in centres with very low inclusion frequencies combined with very brief follow-up times this my also present a potential problem because the outcome of the previous patient may serve as a predictor of the next likely allocation.	**Adequate** **Inadequate** **Unknown**	**Adequate**: when a paper convinces you that allocation cannot be predicted (separate persons, placebo really indistinguishable, clever use of block sizes (large or variable). Adequate approaches might include centralised or pharmacy-controlled randomisation, serially numbered identical containers, on-site computer based system with a randomisation sequence that is not readable until allocation, and other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. **Inadequate**: this option is often difficult. You have to visualise the procedure and think how people might be able to circumvent it. Inadequate approaches might include use of alternation, case record numbers, birth dates or week days, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation) and any other measures that cannot prevent foreknowledge of group allocation. **Unknown**: no details in text. Disagreements or lack of clarity should be discussed in the review team.
3. Were the groups similar at baseline regarding the prognostic factors?		
Baseline characteristics Main aim is to enable the reviewer to see which patients were actually recruited. It enables one to get a rough idea on prognostic comparability. A real check on comparability requires multivariable stratification (seldom shown).	**Reported** **Unknown**	Consult the list of prognostic factors or baseline characteristics (not included in this appendix) Reviewer decides
4. Were the eligibility criteria specified?		

	Adequate **Partial** **Inadequate** **Unknown**	
5. Were the point estimates and measure of variability presented for the primary outcome measure?		
Results for the primary outcome measure	**Adequate** **Partial** **Inadequate** **Unknown**	**Adequate**: mean outcome in each group together with mean difference and its standard error (SE) or standard deviation (SD) or any CI around it or the possibility to calculate those from the paper. Survival curve with log rank test and patient numbers at later time points **Partial**: partially reported **Inadequate**: no SE or SD, or SD without N (SE = SD/N) **Unknown**: very unlikely
6. Did the analysis include an intention to treat analysis?		
Intention-to-treat analysis (ITT) Early drop-out can make this very difficult. Strictest requirement is sensitivity analysis including early drop-outs.	**Adequate** **Inadequate**	Reviewers should not just look for the term ITT but assure themselves that the calculations were according to the ITT principle.
7. Loss to follow-up This item examines both numbers and reasons; typically an item that needs checking in the methods section and the marginal totals in the tables. Note that it may differ for different outcome phenomena or time points. Some reasons may be reasons given by the patient when asked and may not be the true reason. There is no satisfactory solution for this.	**Adequate** **Partial** **Inadequate** **Unknown**	**Adequate**: number randomised must be stated. Number(s) lost to follow-up (dropped out) stated or deducible (from tables) for each group and reasons summarised for each group. **Partial**: numbers, but not the reasons (or vice versa) **Inadequate**: numbers randomised not stated or not specified for each group **Unknown**: no details in text

Appendix 6 Clinical-effectiveness studies – data extraction tables

Reference and Design	Intervention	Participants	Outcome measures
Manns, *et al*, 2001[174] Trial design: RCT (open label) Country: International	<u>Intervention 1:</u> n = 511 PEG IFN α-2b (subcutaneous) Dose: 1.5 µg/kg/wk Duration: 48 wk RBV (oral) Dose: 800 mg/day Duration: 48 wk <u>Intervention 2:</u> n = 514 PEG IFN α-2b (subcutaneous) Dose: 1.5 µg/kg/wk Duration: 4 wk Dose: 0.5 µg/kg/wk Duration: 44 wk RBV (oral) Dose: 1000-1200 mg/day* Duration: 48 wk <u>Intervention 3:</u> n = 505 IFN α-2b (subcutaneous) Dose: 3 million units 3x per wk Duration: 48 wk RBV (oral) Dose: 1000-1200 mg/day* Duration: 48 wk * doses adjusted by body weight – 1000 mg for weight < 75 kg and 1200 mg for weight ≥ 75 kg RBV for all groups administered in two divided doses per day. PEG IFN α-2b administered once per week according to weight	Total numbers involved: 2316 screened, 1530 randomised Eligibility and Exclusion Criteria: see Section 3.2.1 for general criteria plus: • Exclude previous organ transplant, poorly controlled diabetes, autoimmune-type disease Recruitment: 62 centres, worldwide Genotypes (proportions) 1: 68% 2 or 3: 30% 4, 5 or 6: 2% Baseline measurements: Viral Load: HCV RNA in serum – geometric mean copies per mLx10^6: 2.7 No. with > 2x10^6 copies: 1044 (68%) Sex: 1003 male/ 527 female Age (mean & range): 43.3 (21 – 68) Ethnic groups: not reported Losses to follow up: not reported Compliance: not reported	Primary outcomes used: SVR (HCV RNA) Secondary outcomes used: histological response (Knodell histological activity index) Adverse Events Length of follow up: 24 weeks post tx (72 wk from tx initiation)

Outcome	PEG IFN α-2b 1.5 µg/kg + RBV (800 mg)	PEG IFN α-2b 1.5 then 0.5 µg/kg + RBV (1000-1200 mg)	IFN + RBV (1000 – 1200 mg)
Viral Response			
4 wk	--	--	--
12 wk	--	--	--
end of treatment	65% (333/511)*	56% (289/514)	54% (271/505)
SVR	54% (274/511)†	47% (244/514)	47% (235/505)
SVR by genotype			
1	42% (145/348)*	34% (118/349)	33% (114/343)
2 or 3	82% (121/147)	80% (122/153)	79% (115/146)
4, 5, or 6	50% (8/16)	33% (4/12)	38% (6/16)
SVR by ribavirin dose			
≤ 10.6 mg/kg	50% (160/323)	41% (13/32)	27% (6/22)
> 10.6 mg/kg	61% (114/188)	48% (231/482)	47% (229/483)
Biochemical response (alanine aminotransferase)			
end of treatment	65%	63%	69%
sustained response	54%	48%	47%
Histology (proportion with improvement)			
Inflammation	68% (232/339)	70% (254/361)	69% (232/334)
mean change	-3.4	-3.4	-3.4
Fibrosis	21% (71/333)	19% (69/361)	20% (66/328)
mean change	-0.1	-0.2	-0.2
Adverse Events			
dose discontinuation for			
any adverse event	14%	13%	13%
dose reduction for			
any adverse event	42%	36%	34%
anaemia	9%	12%	13%
neutropenia	18%	10%	8%

* $p < 0.05$ compared with IFN + RBV by Fisher's exact test
† $p < 0.05$ compared with IFN + RBV by logistic regression

Additional Results:
- For higher dose of PEG IFN, 75% of patients HCV RNA negative for first time at 12 weeks achieved SVR; 32% HCV RNA negative for first time at week 24 achieved SVR
- Factors associated with SVR:
  (p<0.0001) HCV genotype (other than 1), baseline viral load (lower load), sex, baseline weight (lighter), age (younger)
  (p=0.01) sex (was not a significant factor in a backward elimination procedure)
  (p=0.07) absence of cirrhosis
- Likelihood of SVR increases as ribavirin dose increases.

Methodological comments:
Allocation to treatment groups: Random assignment to groups stratified within groups by HCV genotype (1 v others) and presence or absence of cirrhosis. In blocks of three. Schedule generated by Schering Plough, and performed by an independent central randomisation centre.
Blinding of outcome assessors: Open label trial. Biochemical and haematological testing done by a central laboratory (blinding not specifically mentioned); liver histology analysed by a single blinded pathologist.
Allocation concealment: centralised randomisation by fax

Analysis by intention to treat: yes, for all participants who received at least one dose of study medication
Comparability of treatment groups at pre-treatment: Groups appear comparable, but statistical equivalence not presented.
Method of data analysis: Pairwise treatment comparisons by logistic regression; analyses of changes from baseline by paired student's *t* tests; evaluations of relation of baseline characteristics with treatment response by logistic regression. Power analyses to achieve 90% power to detect a 10% difference in SVR rates at the 5% level of significance required 525 participants per group. Logistic regression to consider relation between baseline disease characteristics and treatment response
Attrition/drop-out: Analyses included all participants who had at least one dose of study medication. Patients with missing HCV RNA values were classified as non-responders

General comments
Generalisability: Participants would appear to be representative of patients with chronic hepatitis C who have not had liver transplant or significant co-morbidities. Authors report that the proportion patients with genotype 1, high viral load, cirrhosis and distributions by age, sex and other characteristics are similar to populations in previous studies.
Conflict of interests: Schering Plough Research Institute study sponsor
Other:
Definitions: SVR = undetectable HCV RNA in serum. Histological response assessed by Knodell histological activity index with improvement in fibrosis = decrease of 1 or more from pre to post-treatment score and worsening = increase of 1 or more from pre to post-treatment score

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	unknown
2. Was the treatment allocation concealed?	adequate
3. Were the groups similar at baseline in terms of prognostic factors?	reported
4. Were outcome assessors blinded to the treatment allocation?	unknown
5. Was the patient blinded?	inadequate
6. Did the analysis include an intention to treat analysis?	adequate
7. Were losses to follow-up completely described?	unknown

Appendix 6 continued

Reference and Design	Intervention	Participants	Outcome measures
Fried, *et al*, 2002 [49] Trial design: RCT Country: International, Pegasys International Study Group	<u>Intervention 1:</u> n = 453 PEG IFN α-2a (subcutaneous) Dose: 180 µg/wk Duration: 48 wk RBV (oral) Dose: 1000 mg/day for patients ≤ 75 kg; 1200 mg/day for patients > 75 kg Duration: 48 wk <u>Intervention 2:</u> n = 224 PEG IFN α-2a Dose: 180 µg/wk Duration: 48 wk placebo (oral) Dose: daily Duration: 48 wk <u>Intervention 3:</u> n = 444 IFN α-2b Dose: 3 million units 3x weekly Duration: 48 wk RBV Dose: 1000 mg/day for patients ≤ 75 kg; 1200 mg/day for patients > 75 kg Duration: 48 wk	Total numbers involved: 1459 screened, 1149 randomised, 1121 received at least one dose of study medication Eligibility & Exclusion criteria: see section Section 3.2.1 for general criteria Recruitment:81 centres, worldwide conducted between Feb 1999 and April 2001 Genotypes (proportions) 1a: 365 (32.5%) 1b: 345 (30.8%) 1 other: 18 (1.6%) 2: 152 (13.6%) 3: 202 (18.0%) 4: 33 (3%) Other: 6 (0.5%) Baseline measurements: Viral Load: Mean HCV RNA level (copies/ml x 10^6): 6.0 Sex: 800 male (71%) / 321 female (29%) Age (mean): 42.5 Ethnic groups: • White: 943 (84.1%) • Black: 53 (4.7%) • Asian: 64 (5.7%) • Other: 61 (5.4%) Cirrhosis: n=144 (13%) Losses to follow up: 28 patients randomised, but did not receive any study medication. Patients who withdrew during wk 1-48: 312 (27.8%) Patients who withdrew during wk 49-72: 39 (3.5%) Compliance: not reported	Primary outcomes used: sustained virological response (HCV RNA at end of follow-up by PCR assay) Secondary outcomes used: Adverse Events Factors associated with SVR Length of follow up: 24 wk

Outcome	PEG IFN α-2a + RBV		PEG IFN α-2a + placebo		IFN α-2b + RBV	
Viral Response						
4 wk	--		--		--	
12 wk[§]	86% (390/453)		--		--	
end of treatment	69% (313/453)*		59% (132/224)[+]		52% (231/444)	
SVR at follow-up	56%* (255/453)		29%[†] (66/224)		44% (197/ 444)	
SVR by genotype						
1	46% (138/298)*		21% (30/145)		36% (103/285)	
2 or 3	76% (106/ 140) [††]		45% (31/69)		61% (88/145)	
4	77% (10/13)		36% (4/11)		44% (4/9)	
5 or 6	--		--		--	
SVR by baseline HCV RNA						
$\leq 2 \times 10^6$ copies/ml	62% (99/159) [††]		46% (32/69)		52% (78/150)	
$> 2 \times 10^6$ copies/ml	53% (156/293) [††]		22% (34/155)		41% (119/292)	
SVR by genotype and baseline HCV RNA						
Genotype 1						
$\leq 2 \times 10^6$ copies/ml	56% (64/115)		39% (17/44)		43% (40/94)	
$> 2 \times 10^6$ copies/ml	41% (76/103)		13% (13/101)		33% (63/189)	
Genotype 2 or 3						
$\leq 2 \times 10^6$ copies/ml	81% (30/37)		58% (11/19)		65% (34/52)	
$> 2 \times 10^6$ copies/ml	74% (76/103)		40% (20/50)		58% (54/93)	
SVR by histological diagnosis						
Cirrhosis	43% (24/56)		21% (7/34)		33% (18/54)	
Adverse Events						
dose discontinuation for						
adverse event	7% (32/453)		5.8% (13/224)		9.7% (43/444)	
laboratory abnormality	2.6% (12/453)		0.9% (2/224)		0.9% (4/444)	
dose reduction for	PEG IFN	RBV	PEG IFN	placebo	IFN	RBV
any adverse event	48 (11%)	95 (21%)	14 (6)	39 (17%)	47 (11%)	97 (22%)
anaemia	4 (1%)	99 (22%)	0	8 (4%)	13 (3%)	83 (19%)
neutropenia	91 (20%)	6 (1%)	38 (17%)	0	24 (5%)	1 (< 1%)
thrombocytopenia	18 (4%)	2 (< 1%)	14 (6%)	1 (< 1%)	1 (< 1%)	0

§ 12 week virological response = 2-log decrease from baseline HCV RNA levels or no detectable serum HCV RNA
* $p \leq 0.01$ for comparisons between PEG + RBV and PEG + placebo and PEG + RBV and IFN + RBV
+ $p = 0.06$ for comparison between PEG + placebo and IFN + RBV
† $p < 0.001$ for comparison between PEG + placebo and IFN + RBV
†† $p < 0.05$ for comparison between PEG + RBV and IFN + RBV

Additional Results (e.g., early response factors adverse events comparisons):

- Three factors independently and significantly increased the odds of achieving a sustained virological response: an HCV genotype other than 1 (odds ratio, 3.25; 95% CI, 2.09 to 5.12, $p < 0.001$); an age of 40 years of less (odds ratio, 2.60; 95% CI 1.72 to 3.95, $p < 0.001$); and a body weight of 75 kg or less (odds ratio, 1.91; 95% CI, 1.27 to 2.89, $p = 0.002$).
- Of those with early virological responses, 65% subsequently had a sustained virological response.
- Those with non detectable HCV RNA by week 12 were more likely to have a sustained virological response than those who had only a 2-log decrease in HCV RNA.
- Among the 63 patients who did not have an early virological response in the PEG + RBV group, 61 (97%) did not have a sustained virological response.
- The proportions of patients withdrawn from treatment because of laboratory abnormalities or other adverse events were similar in all three groups.
- Among patients who had an early virological response on PEG + RBV, the proportion with a sustained virological response was similar among those who had a substantial dose reduction and those who maintained the full dosing schedule.
- Patients treated with PEG had a lower incidence of influenza-like symptoms than those treated with IFN (statistically significant for pyrexia, myalgia and rigors).
- Patients treated with PEG had a lower incidence of depression than those treated with IFN ($p = 0.01$).

Methodological comments:
Allocation to treatment groups: randomly assigned in a 2:1:2 ratio with a block size of five. Randomisation stratified according to country and HCV genotype (HCV genotype 1 vs. other genotypes).
Allocation concealment: not reported

Blinding of outcome assessors: investigators were unaware of who received ribavirin or placebo among patients receiving PEG. No other information about blinding.
Analysis by intention to treat: All patients who received at least one dose of study medication were included in efficacy analyses, and if they had undergone at least one safety assessment after baseline, they were included in the safety analysis. For patients with at least 20 wks of follow-up, the last observed HCV RNA level was used in assessment of efficacy. All patients with follow-up of less than 20 wk were considered to have had no response to treatment.
Comparability of treatment groups at pre-treatment: Baseline characteristics appear similar among groups, but statistical comparisons not reported
Method of data analysis: Cochran-Mantel-Haenszel test was used for all possible pairwise comparisons and global comparisons of the three groups. The test was stratified according to the combination of country and HCV genotype (type 1 vs other genotypes). Stepwise, backward, and multiple logistic regression models were used to explore baseline factors predicting a sustained virological response.
Power analysis: not reported
Attrition/drop-out: 28 participants lost between randomisation and beginning of treatment without explanation, other discontinuations with reasons fully reported. Patients who discontinued therapy prematurely because of intolerance were encouraged to remain in the study
Safety: Patients were withdrawn from treatment if they continued to have vireamia at week 24, if they missed four consecutive doses, or at the discretion of the investigator.

General comments
Generalisability: Patients would appear to be representative of patients with chronic HCV without other co-morbidities.
Conflict of interests: Hoffmann-LaRoche trial sponsors. Data analysis was performed by the sponsor and the authors of this report; the authors had full access to the data, and the decision to publish was not limited by the sponsor.
Other:
Definitions: 12 week virological response

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	unknown
2. Was the treatment allocation concealed?	unknown
3. Were the groups similar at baseline in terms of prognostic factors?	reported
4. Were outcome assessors blinded to the treatment allocation?	Adequate for RBV/inadequate for PEG v IFN
5. Was the patient blinded?	Adequate for RBV/inadequate for PEG v IFN
6. Did the analysis include an intention to treat analysis?	adequate
7. Were losses to follow-up completely described?	adequate

Appendix 6 continued

Reference and Design	Intervention	Participants	Outcome measures
Heathcote, *et al*, 2000[52] Trial design: RCT, open label Country: International, Pegasys International Study Group	<u>Intervention 1:</u> n = 88 IFN α2a Dose: 3 MIU 3x weekly, subcutaneous Duration: 48 wk <u>Intervention 2:</u> n = 96 PEG IFN α2a Dose: 90 µg 1x weekly, subcutaneous Duration: 48 wk <u>Intervention 3:</u> n = 87 PEG IFN α2a Dose: 180 µg 1x weekly, subcutaneous Duration: 48 wk	Total numbers involved: 397 screened, 271 met eligibility criteria and were randomised. Eligibility & Exclusion criteria: see Section Section 3.2.1 for general criteria plus: • biopsy-proved liver cirrhosis or bridging fibrosis Recruitment: 30 centres in USA, Canada, Australia & UK between Sept. 1997 and Oct. 1999 Genotypes (proportions) 1:153 (56.5%) 1a: 88 (32.5%) 1b: 65 (24.0%) 2: 33 (12.2%) 3: 73 (26.9%) 4: 3 (1.1%) Other or unknown: 9 (3.3%) Baseline measurements: Viral Load (10^6 copies/mL): 6.1 Histological Activity Index: 12.96 Sex: 196 male (72.3%), 75 female (27.7%) Age (mean): 47.1 Ethnic groups: • White : 239 (88.2%) • Black: 11 (4.1%) • Asian: 7 (2.6%) • Other: 14 (5.2%) Cirrhosis: 212 (78.2%) Bridging Fibrosis: 58 (21.4%) Losses to follow up: Treatment completed by 64, 78, and 67 pts, respectively and follow-up was completed by 68, 79, and 74 patients. Total loss to follow-up = 50 patients. Compliance:	Primary outcomes used: Sustained virological and biochemical responses Secondary outcomes used: Histological response Length of follow up: 24 wk

Outcome	IFN α2a	PEG IFN α2a 90 µg	PEG IFN α2a 180 µg
Viral Response			
4 wk	--	--	--
12 wk	--	--	--
end of treatment (48 wk)	14% (12/88)	42% (40/96)*	44% (38/87)*
SVR (72 wk)	8% (7/88)	15% (14/96)	30% (26/87)*
ombined virological and biochemical response			
48 wk	10% (9/88)	8% (1/13)	40% (2/5)
72 wk	8% (7/88)	16% (13/83)	29% (24/82)
SVR by genotype			
1	2% (1/47)	5% (3/58)	12% (6/48)
1a	0 (0/28)	4% (1/27)	9% (3/33)
1b	5% (1/19)	6% (2/31)	20% (3/15)
other than 1 or unknown	15% (6/41)	29% (11/38)	51% (20/39)
SVR by HCV RNA level (copies/ml)			
≤ 2,000,000	5% (2/41)	22% (10/45)	37% (16/31)
> 2,000,000	9% (4/45)	8% (4/51)	23% (10/44)
SVR by total HAI score			
≤ 10	0% (0/5)	8% (1/13)	40% (2/5)
> 10	8% (7/83)	16% (13/83)	29% (24/82)
SVR by histological diagnosis			
Cirrhosis	7% (5/67)	14% (11/76)	32% (22/69)
Bridging fibrosis	10% (2/21)	16% (3/19)	22% (4/18)
SVR by genotype and HCV RNA level			
1 & ≤ 2,000,000	0% (0/21)	12% (3/26)	16% (3/19)
	4% (1/25)	0% (0/32)	10% (3/29)
	10% (2/20)	33% (6/18)	55% (12/22)
	20% (4/20)	22% (4/18)	50% (7/14)
1 & > 2,000,000	--	100% (1/1)	50% (1/2)
	--	0% (0/1)	0% (0/1)
other than 1 & ≤ 2,000,000			
other than 1 & > 2,000,000			
unknown & ≤ 2,000,000			
unknown & > 2,000,000			
Histological response wk 72 (proportion with improvement)	31% (17/55)	44% (27/61)	54% (37/68)*
Adverse Events			
dose discontinuation for			
adverse event	8% (7/88)	7% (7/96)	13% (11/87)
laboratory abnormality	2% (2/88)	4% (4/96)	1% (1/87)
dose reduction for			
adverse event	14% (12/88)	2% (2/96)	14% (12/87)
thrombocytopenia	6% (5/88)	18% (17/96)	18% (16/87)
neutropenia	14% (12/88)	9% (9/96)	10% (9/87)

- Additional Results (e.g., early response factors adverse events comparisons):
- A response to therapy at wk 12 predicted an SVR – at wk 12 all of the 26 patients who had an SVR to 180 µg of PEG had had a decrease in viral load by a factor of at least 100 as compared with baseline, and 23 of them had had undetectable HCV RNA.
- A histological response correlated with an SVR – among patient with a virological response at wk 72, 80% of those assigned to receive IFN also had a historical response as did 100% of those assigned to 90 µg of PEG and 88% of those assigned to the 180µg dose of PEG.
- A histological response was seen in 26%, 33%, and 35%, respectively, of patients who did not have an SVR.
- Among patients with a combination of poor prognostic factors (genotype 1 & >2,000,000 copies/ml), 10% of those assigned to 180 µg of PEG and none of those assigned to 90 µg had an SVR.
- More than half of the patients assigned to receive 180 µg of PEG who had paired biopsy specimens had a histological response at wk 72, regardless of the virological or biochemical response.
- Among patients who did not have a virological response, more than 1/3 had histological improvement.
- The proportion of patients with a platelet count below 50,000/mm^3 at any time during treatment was significantly lower among those assigned to IFN (7%) than among those assigned to 90 µg PEG (26%) or 180 µg PEG (19%), p =0.04.
- A higher proportion of the patients assigned to receive 180 µg PEG had myalgia and inflammation at the injection site than of patients in the other two groups.
- Four deaths were reported, but their potential relation to treatment was unclear (one patients assigned to 90µg PEG IFN and three assigned to 180 µg PEG IFN).

Methodological comments:

Allocation to treatment groups: allocation to group according to centre in blocks of 6 patients with random assignments made according to a computer-generated scheme. Patients allocated to groups in a 1:1:1 ratio.
Allocation concealment: not reported
Blinding of outcome assessors: laboratory tests at central laboratories. Pre-treatment biopsies examined without blinding before randomization and were subsequently coded and evaluated in parallel with those obtained at wk 72 by pathologists unaware of treatment assignments.
Analysis by intention to treat: End points (except histological response) were evaluated by intention-to-treat. Two patients assigned to IFN did not receive therapy and one assigned to 180 µg PEG elected alternative therapy, but all were included in ITT analysis. The analysis of histological response included only patients who underwent both pre- and post-treatment biopsies. The analysis of safety included all patients who received at least one dose of study medication and who underwent at least one assessment of safety during the study.
Comparability of treatment groups at pre-treatment: No statistical comparisons were reported, but groups appear comparable.
Method of data analysis: Categorical comparisons of PEG with IFN were made with the Cochran-Mantzel-Haenszel test with stratification according to centre.
Power analysis: not reported
Attrition/drop-out: Patients were withdrawn from the study if they missed four consecutive weeks of treatment or if an investigator was concerned about their safety. Overall, an 18% loss to follow-up was relatively high. Treatment was discontinued in slightly more patients in the IFN group than in the two PEG groups, 27% v 19% and 23% respectively.

General comments:
Generalisability: Patients seem representative of those with HCV and cirrhosis or bridging fibrosis.
Conflict of interests: Trial partially designed by Hoffman-LaRoche who was responsible for monitoring adherence to the International Conference on Harmonization guidelines and for monitoring the analysis of data collected by the investigators.
Other:
Definitions: SVR = undetectable levels of HCV RNA (<100 copies/mL) at the end of the follow-up period. Histological response = decrease of at least 2 point in the total score on the HAI (fibrosis and inflammation combined). The HAI is a 22-point index in which inflammation is graded from 0 (none) to 18 (severe) and fibrosis is graded from 0 (none) to 4 (cirrhosis – 3 indicates bridging fibrosis). If a patient received more than 3 consecutive reduced doses or more than a total of 6 reduced doses, the dose could not subsequently be increased.

* $p < 0.05$ for the comparison with IFN α-2a

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	adequate
2. Was the treatment allocation concealed?	unknown
3. Were the groups similar at baseline in terms of prognostic factors?	reported
4. Were outcome assessors blinded to the treatment allocation?	adequate
5. Was the patient blinded?	inadequate
6. Did the analysis include an intention to treat analysis?	adequate
7. Were losses to follow-up completely described?	adequate

Appendix 6 continued

Reference and Design	Intervention	Participants	Outcome measures
Zeuzem *et al* (2000) [53] Trial design: RCT, open label Country: International Pegasys International Study group	<u>Intervention 1:</u> n = 267 PEG IFN α-2a Dose: 180 µg/wk Duration: 48 wks <u>Intervention 2:</u> n = 264 IFN α-2a Dose: 6MIU 3 x weekly Duration: 12 wks Dose: 3MIU 3 x weekly Duration: 36 wks	Total numbers involved: 613 screened, 531 met inclusion criteria and were randomised Eligibility & Exclusion criteria: see Section 3.2.1 for general criteria plus: ▪ Positive test for anti-HCV antibody ▪ Exclude: Co-infection: Hepatitis A, B; organ transplant; chronic pulmonary disease Recruitment: Patients recruited between December 1997 and November 1999 at 36 centres internationally. Genotypes (proportions) 1a: 163 (30.6%) 1b: 166 (32.4%) 2: 59 (11.1%) 3: 131 (24.6%) 4: 8 (1.5%) Other/unknown: 4 (0.75%) (because of rounding percentages do not add up to 100%) Baseline measurements: Viral Load: Mean number of HCV RNA copies/ml x 10^6 = 7.8 Total HAI score: 8.6-9.0 Cirrhosis: 38 (7.1%) Bridging fibrosis: 32 (6%) No cirrhosis or bridging fibrosis: 460 (87%) Sex: 354 (69%) male Age (mean): 40 years Ethnic groups: ▪ White – 454 (85%) ▪ Black – 11 (2%) ▪ Asian – 50 (9.4%) ▪ Other – 16 (3%) Losses to follow up: Patients who withdrew between wk 1-48: (18%) ▪ PEG IFN α-2a: 44 (16%) ▪ IFN α-2a: 103 (39%) Patients not available at wk 72: 171 (32.2%) ▪ PEG IFN α-2a: 61 (23%) ▪ IFN α-2a: 110 (42%) Compliance: not reported	Primary outcomes: ▪ sustained virological response (HCV RNA at end of follow-up by PCR assay) ▪ Biochemical response (normalisation of serum ALT levels) Secondary outcomes ▪ Histological response (fibrosis, cirrhosis) Length of follow up: 24 weeks post tx (72 wk from tx initiation)

Outcome	PEG IFN α-2a	IFN α-2a
Viral Response		
end of treatment	69%* (95% CI 63-75) (n=185/267)	28% (95% CI 22-33) (n=73/264)
SVR	39%* (95% CI 33-45) (n= 103/267)	19% (95% CI 14-24) (n=50/264)

Histology *(all patients with paired specimens n=351)* % with histological response Mean change in HAI score from Baseline *(patients with a sustained virological response)* % with histological response Mean change in HAI score from baseline	 63% (116) -2.4 82% (95) -4.1	 55% (92) -2.0 86 (79%) -4.9
Adverse Events dose discontinuation dose reduction[†] adverse event laboratory abnormality	 7% (19/265) 8% (21/265) 14% (37/265)	 10% (27/261) 11% (30/261) 9% (24/261)

Additional Results (e.g., early response factors adverse events comparisons):

- Almost all (n=101) of the 103 patients in the PEG group who had an SVR had no detectable HCV RNA or the viral load decreased by a factor of 100 at week 12. In the IFN α-2a group 98% of those who had an SVR had a decrease in viral titer of at least 2 log at week 12.
- Multiple logistic regression analysis identified the following as independently and significantly increasing the odds of a sustained virological response: younger age (<40 years); smaller body surface area (≤2m^2), lower level of HCV RNA; higher ALT quotient; absence of cirrhosis or bridging fibrosis; HCV genotype other than type 1.
- Frequency and severity of adverse events were similar in the two treatment groups.
- There was a high degree of correlation between sustained virological response and biochemical response.

Methodological comments:
Allocation to treatment groups: Random, no further information given
Allocation concealment: No information given
Blinding of outcome assessors: Slides of liver biopsy specimens obtained before the study and 24 weeks after discontinuation of treatment were coded and read by the study pathologist who was unaware of the patients' identity and treatment and date of biopsy. Open label, patient and investigators given 24 week viral results
Analysis by intention to treat: Used for all measures of efficacy except for changes from baseline in histological findings. Patients not present at 72 week assessment were classed as non-responders at that point. Patients who received at least one dose of study medication were included in the analysis of safety.
Comparability of treatment groups at pre-treatment: Authors assert that the baseline characteristics of the patients in the two treatment groups were similar (p. 1667). From data provided in Table 1 on page 1668 groups appear equivalent, although no p-values are given.
Method of data analysis: Cochran-Mantel-Haenszel test for primary efficacy analysis (categorical variables).
Objectives/hypotheses (i) PEG IFN α-2a is equivalent to IFN α-2a (ii) PEG IFN α-2a is superior to IFN α-2a. Multiple and stepwise logistic regression analysis was used to examine the relationship between baseline variables and sustained virological response.
Power analysis: 456 patients were required allowing for a drop out rate of 15% assuming a sustained response rate of 25% in the IFN α-2a group and 35% in the PEG IFN α-2a group.
Attrition/drop-out: Even though an ITT analysis was performed, the loss to follow up rate is relatively high (32%). Note that withdrawal and loss to follow-up rates are higher in the IFN α-2a group, which suggest that PEG IFN α-2a is maybe more acceptable to patients.

General comments:
Generalisability: Authors comment that the baseline characteristics of the groups in this study are similar to patients in the two large trials evaluating the effectiveness of dual therapy with IFN α-2.
Conflict of interests: Data analysis was performed by Hoffmann-LaRoche in conjunction with the authors.

* statistically significant difference ($p<0.05$) for comparison with IFN α-2a
[†] Some patients who required dose modification had both an adverse event and a laboratory abnormality

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were outcome assessors blinded to the treatment allocation?	Adequate
5. Was the patient blinded?	Partial
6. Did the analysis include an intention to treat analysis?	Adequate

7. Were losses to follow-up completely described?	Partial

Appendix 6 continued

Reference and Design	Intervention	Participants	Outcome measures
Lindsay, *et al*, 2001[51] Trial design: RCT Country: International	Intervention 1: n = 315 PEG IFN □2b Dose: 0.5 µg/kg, 1x/wk, subcutaneous Duration: 48 wk Intervention 2: n = 297 PEG IFN α-2b Dose: 1.0 µg/kg, 1x/wk, subcutaneous Duration: 48 wk Intervention 3: n = 304 PEG IFN α-2b Dose: 1.5 µg/kg, 1x/wk, subcutaneous Duration: 48 wk Intervention 4: n = 303 IFN α-2b Dose: 3MIU, 3x/wk, subcutaneous Duration: 48 wk	Total numbers involved: 1224 initially randomised. 1219 received at least 1 dose of study medication and were included in analyses; 5 were not treated for reasons unrelated to the study. Eligibility & Exclusion criteria: see Section 3.2.1 for general criteria Exclusion criteria: • Any other cause for liver disease • HIV infection • Haemophilia • Haemoglobinopathies • Active substance abuse • Any known pre-existing medical condition that could interfere with participation • Pregnant or breastfeeding Recruitment: 53 study sites worldwide. Study conducted from Aug, 1997 to Aug, 1999. Genotypes (proportions) 1: 851 (69.8%) 2: 125 (10.2% 3: 200 (16.4%) Other: 43 (3.5%) (because of rounding percentages do not add up to 100%) Baseline measurements: Viral Load: geometric mean copies x10^6/ml: 3.35 > 2 million copies/mL serum: 903 (74.1%) Mean HAI (Knodell) score: Inflammation: 6.9 Fibrosis: 1.4 Bridging fibrosis: 164 (13.4%) Cirrhosis: 43 (3.5%) Sex: 770 male (63.2%), 449 female (36.8%) Age (mean): 43.0 Ethnic groups: Caucasian: 1109 (91%) Losses to follow up: Of 1219 treated patients, 943 (77%) competed the 72-wk study. Pre- and post-treatment liver biopsies were analysed in 61% (744/1219) patients. Compliance:	Primary outcomes used: Sustained virological response Secondary outcomes used: Normalisation of ALT and improvement of liver histology Length of follow up: 24 wk

Outcome	PEG IFN α-2b 0.5 µg/kg	PEG IFN α-2b 1.0 µg/kg	PEG IFN α-2b 1.5 µg/kg	IFN α-2b 3 MIU
Viral Response				
4 wk	--	--	--	--
12 wk	--	--	--	--
end of treatment (48 wk)	33% (105/315)*	41% (121/297)*	49% (149/304)*	24% (73/303)
SVR (72 wk)	18% (57/315)*	25% (73/297)*	23% (71/304)*	12% (37/303)
Combined Virological and biochemical response				
48 wk	25% (79/315)	31% (92/297)*	33% (100/304)*	20% (61/303)
72 wk	17% (52/315)	24% (70/297)*	23% (69/304)*	12% (37/303)
SVR by genotype and baseline viral load (wk 72)				
1 (all)	10% (12/211)	14% (28/199)	14% (31/223)	6% (14/217)
≤ 2 million copies	27% (14/52)	38% (16/42)	34% (19/56)	21% (10/48)
> 2 million copies	5% (8/159)	8% (12/157)	7% (12/167)	2% (4/169)
2 or 3 (all)	35% (31/88)	47% (39/83)	49% (36/73)	28% (23/81)
≤ 2 million copies	58% (14/24)	62% (13/21)	68% (15/22)	36% (9/25)
> 2 million copies	27% (17/64)	42% (26/62)	41% (21/51)	25% (14/56)
4, 5, or 6 (all)	20% (2/10)	31% (4/13)	60% (3/5)	0/4
≤ 2 million copies	33% (2/6)	50% (4/8)	75% (3/4)	0/2
> 2 million copies	0/4	0/5	0/1	0/2
Histology (proportion with improvement)				
Inflammation	49% (97/098)	50% (89/178)	48% (85/177)	47% (90/191)
mean change	-1.5	-1.8	-1.5	-1.2
Fibrosis	20% (40/198)	19% (34/178)	15% (27/177)	13% (25/191)
mean change	-0.1	0	0.1	0.1
Relapse rate by genotype and baseline viral load	Not reported	46% (23/50)‡ 17% (3/18) 63% (20/32) 38% (24/63) 19% (3/16) 45% (21/47)	66% (57/87)‡ 36% (10/28) 80% (47/59) 36% (20/56) 12% (2/17) 46% (18/39)	Not reported
1 (all)				
≤ 2 million copies				
> 2 million copies				
2 or 3 (all)				
≤ 2 million copies				
> 2 million copies				
Adverse Events				
dose discontinuation	9%	11%	9%	6%
dose reduction		14%	19%	6%
dose reduction for thombocytopenia	9%	2% - 3%	2% - 3%	0.3%
dose reduction for neutropenia	2% - 3% 2% - 3%	2% - 3%	5%	2% - 3%

‡ comparison between 1.0 and 1.5 µg/kg doses, $p = 0.26$
* $p < 0.05$ for comparison with IFN

Additional Results:

- Logistic regression analysis identified only 2 covariates associated with SVR: HCV genotype other than 1 and baseline HCV RNA levels of ≤ 2 million copies/mL serum, $p < 0.001$.
- In each treatment group, the likelihood of an SVR occurring was highest in patients whose first negative HCV RNA occurred at treatment week 4 (77%-86%), compared with those in whom HCV RNA was first negative at treatment week 12 (32% - 52%), and those whose HCV RNA was first negative at treatment week 24 (13% -20%).
- Nearly all patients who eventually became sustained responders had developed undetectable serum HCV RNA by treatment week 24 (93% - 100%).
- Negative predictive values (the likelihood that an SVR would occur if HCV RNA was not detected) for treatment wk 4 were 85% and 77% respectively for patients treated with 1.0 µg/kg and 1.5 µg/kg PEG IFN.
- Positive predictive value (the likelihood that an SVR would not occur if HCV RNA was detected) at treatment wk 4 was 84% and 90%, respectively for 1.0 µg/kg and 1.5 µg/kg PEG.
- The incidence of injection site reactions was approximately twice the level in patients treated with PEG as in those treated with IFN.

Methodological comments:
Allocation to treatment groups: randomised into groups, but no further information
Allocation concealment: not reported
Blinding of outcome assessors: study double-blinded for all PEG doses. Assays performed by a central laboratory. Liver biopsies scored by single blinded pathologist.
Analysis by intention to treat: Efficacy assessments were obtained in all patients who were randomised and received at least 1 dose of study drug (n=1219)
Comparability of treatment groups at pre-treatment: There was a higher proportion of patients with genotype 1 in the 1.5 µg/kg group (73%) than to the 1.0 and 0.5 µg/kg groups (67% in each, $p = 0.09$).
Method of data analysis: SVR for PEG v IFN by χ^2. Baseline characteristics compared using Kruskal-Wallis test. Relation of baseline characteristics and treatment response evaluated by logistic regression.
Power analysis: not reported
Attrition/drop-out: Efficacy results based on all patients receiving at least one dose. Number discontinuing treatment reported, but reasons not reported. Overall, 23% of patients not completing the study was relatively high, but the report states that discontinuation rates were comparable across all treatment groups.

General comments
Generalisability: Patients seem representative of European patient populations with high percentage of genotype 1 and high baseline HCV RNA levels.
Conflict of interests: supported in part by Schering Plough
Other:
Definitions: Virological response = loss of detectable serum HCV RNA (<100 copies/mL) at any time during study. SVR = undetectable levels of HCV RNA 24 weeks after treatment. Relapse = undetectable serum levels of HCV RNA at end of treatment and detectable levels at 24 wk follow-up. Improved inflammatory score = decrease of ≥ 2 units. Improved fibrosis score = decrease of ≥ 1 unit.

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	unknown
2. Was the treatment allocation concealed?	unknown
3. Were the groups similar at baseline in terms of prognostic factors?	partial
4. Were outcome assessors blinded to the treatment allocation?	adequate
5. Was the patient blinded?	Adequate for PEG doses
6. Did the analysis include an intention to treat analysis?	adequate
7. Were losses to follow-up completely described?	partial

Appendix 6 continued

Reference and Design	Intervention	Participants	Outcome measures
Reddy,*et al*, 2001[40] Trial design: RCT (3 cohorts), open-label Country: USA	Intervention 1: n = 33 IFN α-2a Dose: 3 MIU 3x weekly Duration: 48 wk Intervention 2: n's = 20, 20, 45, 41 PEG IFN α-2a Dose: 45, 90, 180, or 270 µg Duration: 48 wk	Total numbers involved: 159 Eligibility & Exclusion criteria: see Section 3.2.1 for general criteria plus: • CHC without bridging fibrosis or cirrhosis (15 patients with bridging fibrosis inadvertently included) • Exclude fibrosis score 3 and 4 • Exclude hx of pre-existing medical conditions such as unstable thyroid dysfunction or renal disease • Exclude therapy with systemic antineoplastic or immunomodulatory agents within the past 6 mo or administration of antiviral or investigational compounds within the past 3 mo Recruitment: multi-centre, 3 successive cohorts with ascending doses of PEG IFN α-2a were recruited (45 or 90 µg of PEG v IFN then 180 µg of PEG v IFN then 270 µg of PEG v IFN). Randomisation to PEG v IFN in 4:1 ratio. Conducted Feb 1997 to March 1999. Genotypes (proportions) 1: 73.6% Non-1: 23.9% Missing: 2.5% Baseline measurements: Viral Load (10^6 copies/mL): 2.4 Total HAI score (for patients with paired pre & post-treatment biopsies): Mean = 10.4; median = 10.0 – 12.0 across treatment groups Sex: 125 male (79%), 34 female (21%) Age (mean): 42.0 Ethnic groups: • White: 139 (87%) • Black: 14 (9%) • Oriental: 2 (1.3%) • Other: 4 (2.5%) Bridging Fibrosis: 15 (9.4%) (patients with bridging fibrosis were to be excluded, but these were inadvertently enrolled) Losses to follow up: 122 completed 48 wk of treatment. 23 were withdrawn due to adverse events.	Primary outcomes used: Sustained virological response (proportion of patients with < 100 copies/mL HCV RNA at wk 72) Secondary outcomes used: Sustained biochemical response at wk 72, virological and biochemical responses at wk 48, histological response Length of follow up: 24 wk

Outcome	IFN α-2a 3 MIU	PEG IFN α-2a 45 µg	PEG IFN α-2a 90 µg	PEG IFN α-2a 180 µg	PEG IFN α-2a 270 µg
Viral Response					
4 wk	--				
12 wk	--				
end of treatment (48wk)	12% (4/33)	30% (6/20)	45% (9/20)*	60% (27/45)*	56% (23/41)*
SVR	3% (1/33)	10% (2/20)	30% (6/20)*	36% (16/45)*	29% (12/41)*
SVR by genotype					
1	4% (1/25)	7% (1/15)	14% (2/14)	31% (11/35)	12% (3/26)
Non-1	0 (0/4)	20% (1/5)	67% (4/6)	50% (5/10)	67% (8/12)
Other Viral Response outcomes					
Histology (in patients with paired pre- and post-treatment biopsies)					
Change from baseline mean total HAI score	-2.0 ± 0.6	-0.9 ± 0.8	-2.6 ± 1.0	-2.8 ± 0.6	-2.5 ± 0.7
Change from baseline median total HAI score	-2.0	-1.0	-2.0	-3.0	-2.0
Proportion of histological responders	57% (13/23)	47% (7/15)	59% (10/17)	63% (19/30)	66% (19/29)
Adverse Events					
% reported as severe	10%	7%	2%	10%	7%
Withdrawn for adverse events or laboratory abnormalities	9%	10%	0%	22%	20%
dose reduction for					
any adverse event					49% (20/41)
anaemia					
neutropenia					

Additional Results (e.g., early response factors adverse events comparisons):

- SVR increased in a dose-dependent manner between 45 and 180 µg PEG with no further increase in response at the 270 µg dose.
- Most patients (94/159) who achieved a virological response did so within the first 16 weeks of treatment, particularly those in the 180 and 270 µg dose groups (78% and 73%, respectively).
- Of the patients with paired biopsies who achieved sustained virological responses, all but 2 (in 270 µg group) also achieved histological responses.
- Among the 88 patients with paired biopsies who did not have a SVR, between 42% and 60% in the PEG groups and 55% in the IFN group achieved a histological response.
- Depression, pruritus and irritability were reported in a higher percentage of patients in the PEG groups compared with the IFN group.
- Treatment with PEG was associated with mild, dose-dependent decreases in haemoglobin (<12 g/dL), but median haemoglobin concentrations remained within the normal range throughout the treatment period, and no patients discontinued because of anaemia.

Methodological comments:

Allocation to treatment groups: randomised within 3 cohorts in which patients were assigned to 45 or 90 µg PEG or IFN (cohort 1), 180 µg PEG or IFN (cohort 2), 270 µg PEG or IFN (cohort 3). Initial safety data (8 weeks) were reviewed by an independent safety review board for each cohort before successive cohorts were randomised to higher doses of PEG. Open-label
Allocation concealment: not reported
Blinding of outcome assessors: Open-label. Virological and biochemical assays were performed at a central laboratory. Histological response evaluated by a central pathologist in a coded, blinded fashion.
Analysis by intention to treat: efficacy analyses included all randomised patients, including 4 patients who were not treated. Safety analyses included all patients who received at least 1 dose of study medication and had at least 1 post-baseline safety assessment.
Comparability of treatment groups at pre-treatment: Statistical comparisons were not reported. IFN group had the highest proportion of patients with genotype 1, a higher mean HCV-RNA concentration, and more patients with cirrhosis and bridging fibrosis. This group also had more non-white patients.
Method of data analysis: Fisher's exact test was used to compare biochemical, virological, and histological responses between PEG and IFN groups.
Power analysis: not reported
Attrition/drop-out: 23% of randomised patients did not complete 48 weeks of treatment. There was no information as to whether these were equally distributed between treatment groups. 23 patients (14.4%) were prematurely withdrawn from the trial due to adverse events. Withdrawals due to adverse events were higher in the 180 µg and 270 µg PEG groups than the other treatment groups.

General comments
Generalisability: Patients seem representative of patients with CHC without severe liver disease (no cirrhosis or bridging fibrosis) or other co-morbidities.
Conflict of interests: One author employed by Hoffmann-LaRoche, Inc.
Other:
Definitions: CHC required documentation of persistently abnormal serum alanine aminotransferase activity (2 occasions ≥ 14 days apart), a positive anti-HCV antibody (anti-HCV-EIA version 2), pre-treatment liver biopsy obtained within 12 mo before study treatment consistent with chronic hepatitis and detectable pre-treatment HCV RNA by a polymerase chain reaction assay within 35 days before the first dose of study medication. Histological response = ≥ 2-point decrease in the total histological activity index (HAI) between biopsies obtained at baseline and wk 72.

*p < 0.05 in comparison with IFN α-2a group

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	unknown
2. Was the treatment allocation concealed?	unknown
3. Were the groups similar at baseline in terms of prognostic factors?	partial
4. Were outcome assessors blinded to the treatment allocation?	adequate
5. Was the patient blinded?	inadequate
6. Did the analysis include an intention to treat analysis?	adequate
7. Were losses to follow-up completely described?	partial

Appendix 7 Data Extraction for meta-analysis of trials assessing histological improvement

Reference and Design	Intervention	Participants	Outcome measures
Poynard *et al*, 2002[64] Trial design: pooled data from Lindsay, *et al*, 2001[51]; Manns, *et al*, 2001[155]; Poynard, *et al*, 1998[155]; & McHutchison, *et al*, 1998[155] Country:	<u>10 regimens compared:</u> 'Control' regimen: • IFN α-2b, 3MIU 3x/wk, 24 wk 'Reinforced 'regimens: • IFN α-2b, 3MIU 3x/wk, 48 wk • PEG α-2b 0.5 µg/kg, 48 wk • PEG α-2b 1.0 µg/kg, 48 wk • PEG α-2b 1.5 µg/kg, 48 wk • IFN + RBV(1000 mg if wt < 75kg, 1200 mg if wt ≥ 75 kg), 24 wk • IFN + RBV, 48 wk • PEG α-2b 1.5 for 1 mo then 0.5 PEG + RBV (1000 mg if wt < 75kg, 1200 mg if wt ≥ 75 kg) • PEG α-2b 1.5 + low dose RBV (10.6 mg/kg or less) • PEG α-2b 1.5 + high dose RBV (more than 10.6 mg/kg)	Total numbers involved: individual data from 3010 treatment naïve patients Eligibility: patients with serologic confirmation of chronic hepatitis C with both pre-treatment and post-treatment liver biopsies. Exclusion criteria: HBV, HIV, daily alcohol consumption > 50g or other forms of liver disease	Primary outcomes used: Changes in METAVIR necrosis and inflammation score

Results:

- The SVR varied from 5% (IFN, 24wk) to 63% (PEG 1.5 + high dose RBV)
- Fibrosis stage improved in 20% of patients, was stable in 65% and worsened in 15%.
- Among patients who achieved an SVR, there was less frequently worsening of fibrosis (7%) in comparison with relapsers (17%) or non-responders (21%), $p < 0.001$ for both comparisons. There was also more activity improvement in those with SVR (86%) vs 43% and 36%, respectively, p's < 0.001. Relapsers also significantly differed from non-responders.
- In histological response, there were highly significant differences between regimens. Fibrosis worsening ranged from 8% in patients receiving the PEG 1.5 + RBV high dose combination to 23% in patients treated with IFN for 24 weeks. Activity improvement ranges from 73% in patients receiving the PEG 1.5 and high dose RBV to 39% in patients treated with IFN for 24 weeks.
- All rates of fibrosis progression were lower after treatment than before both in responders and in non-responders (p's < 0.001). There were no significant differences between different treatments. There was a significant different between responders and non-responders.
- Six factors were independently associated with the absence of significant fibrosis after treatment: baseline fibrosis stage (OR = 0.12, $p < 0.0001$), SVR (OR= 0.36, p, < 0.0001), age younger than 40 (OR = 0.51, $p <$ 0.001), BMI < 27 kg/m^2 (OR = 0.65, p, < 0.001), no or mild baseline activity (OR = 0.70, $p = 0.02$), and viral load lower than 3.5 million copies/mL (OR = 0.79, $p = 0.03$).
- In patients without SVR (relapsers and non-responders), in comparison with the other regimens, PEG 0.5 +RBV had a better impact on fibrosis and on activity with 21% having demonstrable fibrosis improvement vs 12% for 24wk IFN, p =0.04 and vs 15% for 48 wk IFN. Activity improvement was also best in the 0.5 PEG + RBV group with 50% improvement activity with other regiments ranging from 33% to 44% improved activity.
- The 'reversal' of cirrhosis was observed in 75 patients of the 153 who had cirrhosis at the time of their first biopsy. None of these were in the 24 wk IFN regimen.

General comments

Four comparisons were addressed:

- Compared the impact of the different treatment regimens on the percentage of patients who improve by at least 1 fibrosis stage, remained stable or worsened by at least 1 stage.
- Compared the different treatment regimens according to the fibrosis progression rates per year before and after treatment.
- Assessed the impact of the different treatment regimens adjusted by other risk factors in multi-variate analyses with the end point the percentage of patients with significant fibrosis at the second biopsy.
- Tested the hypothesis that the 'reinforced' regimens can reverse cirrhosis in comparison with the 'control' regimen.

Generalisability:

Conflict of interests:

Other:

Definitions: Liver biopsies evaluated for stage of fibrosis according to METAVIR scoring system with fibrosis staged on scale of 0 to 4 and the grading of necroinflammatory activity scored on a 3 point scale. Fibrosis progression rate after treatment was the ratio between the difference in fibrosis stage expressed in METAVIR units between the 2 biopsies and the interval between the 2 biopsies in years. The progression rate before treatment was the ratio between the fibrosis stage in METAVIR units before the biopsy before treatment and the estimated duration of infection in years. One grade in METAVIR is equivalent to 4 grades in the Knodell index and is twice the usual definition of histological improvement.

Appendix 8 Search strategy – Hepatitis C – Re-treatment of non-responders to interferon alpha monotherapy with dual therapy (interferon alpha and ribavirin)

Databases	Date & years searched	Search strategy	Number retrieved	Number downloaded
Medline	2001-2003/01 5/02/03	((hepatitis-c or HCV) or (explode 'Hepatitis-C' / all subheadings in MIME,MJME) or ('Hepacivirus-' / all subheadings in MIME,MJME)) and (((explode 'Interferons-' / all subheadings in MIME,MJME) or (explode 'Interferon-Type-I' / all subheadings in MIME,MJME) or (explode 'Interferon-Type-II' / all subheadings in MIME,MJME) or (explode 'Interferon-alpha' / all subheadings in MIME,MJME) or (interferon alpha in ti,ab) or (interferon alfa in ti,ab) or (interferon*) or (Roferon-A or Viraferon)) or (mono?therapy)) and ((('Ribavirin-' / all subheadings in MIME,MJME) or (ribav?rin) or (rebetol)) or ('Combined-Modality-Therapy' / all subheadings in MIME,MJME) or (dual therapy or combination therapy) or (explode 'Drug-Therapy-Combination' / all subheadings in MIME,MJME)) and ((non adj respon*) or (non?respon*))	89	35 RCTs or SRs
Embase	2001/7-2003/01	((('ribavirin-' / all subheadings) or ('rebetron-' / all subheadings) or (ribav?rin) or (rebetol)) or (dual adj therapy) or (combination adj therapy) or (explode 'drug-combination' / all subheadings)) and (((explode 'interferon-' / all subheadings) or	80	18 SRs 59 RCTs

		(interferon*) or (roferon-A or viraferon)) or (mono adj therapy)) and (('hepatitis-C' / all subheadings) or (hepatitis-c or hcv)) and ((non adj respon*) or non?respon*)		
Science Citation Index (SCI)	2001-2003	Title=hepatitis-c and interferon* and (nonrespon* or non respon*); DocType=All document types; Language=All languages;	88	87
Cochrane	Issue 2003/1 Search limited from 2001	hepatitis-c or hcv and interferon* and (non-respon* or nonrespon*)	33 Central 3 CDSR 1 Protocol 2 DARE 2 NHS EED	26 Central

Appendix 9 Assumptions used in the base case cost-effectiveness/cost-utility analysis

Economic assumption	Figure	Evidence
Unit costs		
Cost of attendance at general practice	£18	NHS Southampton Trust (See Appendix 10)
Average cost out-patient visit to general medicine	£66	NHS Southampton Trust (See Appendix 10)
Average cost per in-patient day in general medical ward	£133	NHS Southampton Trust (See Appendix 10)
Cost for PEG IFN 2a (180µg per week)	£162	BNF 44
Cost per 10MIU vial interferon alpha 2b (Intron A™) (dose = 3 x 3MIU per week)	£53	BNF 44
Cost for 6 x 200mg capsules of ribavirin (Rebetol™) per day (dose = 1,200mg per day)	£148.20	BNF 44
Cost for 4 x 200mg capsules of ribavirin (Rebetol™) per day (dose = 800mg)	£118	BNF 44
Resource Costs		
Annual average cost with HCC (based on 60 in-patient days in general medicine)	£7, 980	duration of stay based on clinical opinion
Annual average cost with cirrhosis (based on 3 out-patient attendances and 3 general practice visits)	£252	frequency of visits based on clinical opinion
Annual average cost associated with chronic HCV infection (based on 1 visit to out-patients in general medicine and 2 GP associated visits)	£102	Based on 1 out patient attendance and 2 general practice visits (clinical opinion)
Annual average cost associated with ascites (based on 49 in-patient days in general medicine)	£6, 517	duration of stay based on clinical opinion
Annual average cost associated with hepatic encephalopathy (based on 49 in-patient days in general medicine)	£6, 517	duration of stay based on clinical opinion
Annual average cost associated with variceal bleeds (based on 14 in-patient days in general medicine)	£1, 862	duration of stay based on clinical opinion
Cost of liver transplant and follow up care	£46, 551	National contract cost
Discount rate for costs and benefits	3%	Treasury discount rates

Utilities used in the cost-utility analysis		
Health State	Utility	Evidence
Anti-viral treatment	1.00	Assumption
Chronic hepatitis	0.92	Wong *et al.* 2000[142]
Cirrhosis	0.82	Wong *et al.* 2000[142]
Ascites	0.52	Wong *et al.* 2000[142]
Hepatic encephalopathy	0.55	Wong *et al.* 2000[142]
Variceal bleeds	0.50	Assumption
Liver transplant	0.86	Wong *et al.* 2000[142]
HCC	0.55	Wong *et al.* 2000[142]

Appendix 10 Costs of investigation and monitoring of patients with chronic hepatitis C

These costs have been provided by the Finance Department of Southampton University Hospitals Trust and are provided to allow an estimate of approximate costs and facilitate comparison with individual Trust/Authority data. The cost of initial evaluation of a patient, further investigation, and monitoring during and after treatment are likely to be the same whether pegylated or non-pegylated interferon is given. However, there may be some variation n the timing and nature of investigations. There is likely to be some regional variation in the costs for some of the tests.

Costs are measured according to the opportunity cost principle. To make costs comparable between different treatment alternatives fixed costs, which can not be saved if the treatment is not carried out, should then be excluded from the analysis. Included costs, therefore, are mainly direct operating costs plus costs for possible expensive equipment paid by the operating budget."

Evaluation of a new patient with confirmed HCV

ITEM		**COSTS (£)**
Outpatient appointment:		
Time with nurse - 1 hour (Grade H assumed)	£16.56	£16.56
Time with doctor - 20 mins (Consultant assumed)	£46.35	£15.45
Total staff time		£32.01
Overheads for clinic administration (pulling notes etc)	10%	£3.20
STAFF cost for outpatient appointment		£35.21
Tests and investigations		
Hepatitis C Screen (HCV RNA)	Virology	£11.33
HBV (for 50% of patients)	Virology	£5.18
LIVER FUNCTION TESTS	Chem Path	£3.60
ALPHA - FETOPROTEIN (cirrhotic patients - 15%)	Chem Path	£1.31
ALPHA - ANTITRYPSIN	Chem Path	£5.50
TSH	Chem Path	£3.60
FREE T4	Chem Path	£3.60
FULL BLOOD COUNT	Haematology	£2.20
AUTOANTIBODIES	Immunology	£22.30
IMMUNOGLOBULINS	Immunochemistry	£2.20
FERRITIN	Haematology	£10.00
CAERULOPLASMIN	Chem Path	£6.60
IRON	Chem Path	£4.30
U & E'S (including renal profile and urea)	Chem Path	£5.60
INR	Haematology	£2.40
GLUCOSE	Chem Path	£2.50
FBC	Haematology	£2.20
Ultrasound scan of liver	Radiology	£48.00
Chest X-ray	Radiology	£15.00
ECG		£31.00
Cryoglobulin	Immunochemistry	£11.90
Pulmonary function tests (estimated 5% of patients)		£1.00
TOTAL		**£236.53**

FURTHER INVESTIGATIONS OF A PATIENT WITH HCV CONSIDERED FOR TREATMENT

ITEM		COSTS (£)
Outpatient visit:		
To review results from above tests and brief on treatment options		
Time with nurse - 20 mins (Grade H assumed)	£16.56	£5.52
Time with doctor - 20 mins (Consultant assumed)	£46.35	£15.45
Overheads for clinic administration (pulling notes etc)	10%	£2.10
STAFF cost for outpatient appointment		£23.07
HCV QUANTITATIVE PCR	Molecular path	£152.27
HCV GENOTYPE	Not done at SUHT	£148.00
Pregnancy test (estimated 5% of patients)	Chem Path	£0.25
Daycase for liver biopsy:		
Additional tests undertaken prior to biopsy:		
FBC	Haematology	£2.20
INR	Haematology	£2.40
Blood group	Haematology	£2.20
Ultrasound guided biopsy (by Radiologists)	Radiology	£173.00
Liver biopsy costs in Pathology	Histopathology	£126.00
Clerking in patient - 30 mins Grade D nurse assumed	£10.18	£5.09
Ward time for recovery post-biopsy - 6 hours		£18.66
Additional costs for time on ward estimated at 10%		£1.87
TOTAL		£655.00

Monitoring during 24 weeks of treatment

ITEM		COSTS (£)
1st appointment:		
Time with nurse -120 mins (Grade H assumed)	£16.56	£33.13
Time with doctor - 10 mins (Consultant assumed)	£46.35	£7.72
Overheads for clinic administration (pulling notes etc)		£4.09
STAFF cost for outpatient appointment		£44.94
FBC	Haematology	£2.20
INR	Haematology	£2.40
U&Es	Chem Path	£5.60
LFT	Chem Path	£3.60
HCV QUANTITATIVE VIRAL LOAD	Molecular path	£152.27
Pregnancy test (5% of patients)	Chem Path	£0.25
Total for 1st treatment appointment		**£211.25**
SUBSEQUENT APPOINTMENTS:		
Basic checks (at weeks 1,2,6,16 and 20)		
Time with nurse - 30 mins (Grade H assumed)	£16.56	£8.28
Time with doctor - 5 mins (Consultant assumed)	£46.35	£3.86
Overheads for clinic administration		£1.21
Staff cost for appointment		£13.36
FBC	Haematology	£2.20
U&Es	Chem Path	£5.60
LFT	Chem Path	£3.60
Pregnancy test (week 16+20)		£0.25

Total for each basic assessment		**£25.00**
Hence total cost for basic assessments		£125.02
More detailed assessment (at weeks 4 and 8)		
Time with nurse - 30 mins (Grade H assumed)	£16.56	£8.28
Time with doctor - 5 mins (Consultant assumed)	£46.35	£3.86
Overheads for clinic administration		£1.21
Staff cost for appointment		£13.36
FBC	Haematology	£2.20
U&Es	Chem Path	£5.60
LFT	Chem Path	£3.60
INR	Haematology	£2.40
Pregnancy test (5% of patients)	Chem Path	£0.25
Total for 4 and 8 week assessment		**£27.40**
Hence total cost for 4 & 8 week assessments		£54.81
Detailed assessment (week 12)		
Time with nurse - 30 mins (Grade H assumed)	£16.56	£8.28
Time with doctor - 10 mins (Consultant assumed)	£46.35	£7.72
Overheads for clinic administration		£1.60
Staff cost for appointment		£17.61
FBC	Haematology	£2.20
U&Es	Chem Path	£5.60
LFT	Chem Path	£3.60
INR	Haematology	£2.40
TFT (Thyroid function tests)	Chem Path	£13.30
AFP (cirrhotic patients - 15%)	Chem Path	£1.31
HCV VIRAL LOAD	Molecular Path	£152.27
Pregnancy test (5% of patients)	Chem Path	£0.25
Total cost for 12 week assessment		**£198.53**
Detailed assessment (week 24)		
Time with nurse - 30 mins (Grade H assumed)	£16.56	£8.28
Time with doctor - 15 mins (Consultant assumed)	£46.35	£11.59
Overheads for clinic administration (10%)		£1.99
Staff cost for appointment		£21.86
FBC	Haematology	£2.20
U&Es	Chem Path	£5.60
LFT	Chem Path	£3.60
INR	Haematology	£2.40
TFT	Chem Path	£13.30
AFP	Chem Path	£1.31
HCV RNA (Qualitative)	Virology	£11.33
Ultrasound of liver (cirrhotic patients only)	Radiology	£7.20
Pregnancy test (5% of patients)	Chem Path	£0.25
Total cost for 24 week assessment		**£69.03**

Monitoring during interferon alpha treatment (48 weeks)

All patients would receive the treatments as per the 24 week patients	
First appointment	£211.25
Basic assessments (weeks 1,2,6,16 and 20)	£125.02
Week 4 and week 8 assessments	£54.81
Week 12 assessment	£198.53
Week 24 assessment	£69.03
Total	£658.63
Subsequent assessments:	

Weeks 28, 32, 40 & 44 (as basic assessments, plus pregnancy test)	
Per assessment	£25.25
Total assessments	£100.99
Week 36 (as week 12, excluding Viral load)	£46.26
Week 48 (as week 24)	£69.03

Total monitoring cost for 48 week patient	**£874.92**

Surveillance of patients failing, refusing or unsuitable for treatment (per year)

ITEM		**COSTS (£)**
3 OUT PATIENT APPOINTMENTS:		
Staff costs - assumes 20 minutes per appointment with doctor or nurse(alternates - average cost is taken)	£16.56 £46.35	£31.45
ALT 3 * PER YEAR		£10.80
Liver function tests		£10.80
ALPHA - FETOPROTEIN 3 * ANNUALLY		£3.92
INR (twice per year)		£4.80
Tests for cirrhotic patients only (estimated 15% pats)		
Liver ultrasound *2		£14.40
Additional OP appointment (4 per year)		£8.55
TOTAL FOR YEAR		**£84.72**

NB commitment to caring for these patients will be long-term

Surveillance of patients following response after one year of treatment completed (per year)

ITEM		**COSTS (£)**
4 weeks post treatment		
Staff costs - assumes 20 minutes per appointment with doctor or nurse(alternates - average cost is taken)		£10.48
Overheads for clinic administration @ 10%		£1.05
Total staff costs		£11.53
FBC	Haematology	£2.20
INR	Haematology	£2.40
U & Es	Chem Path	£5.60
LFT	Chem Path	£3.60
Pregnancy test (5%)	Chem Path	£0.25
TOTAL		**£25.58**
12 weeks post treatment		
Staff costs - assumes 20 minutes per appointment with doctor or nurse(alternates - average cost is taken)		£10.48
Overheads for clinic administration @ 10%		£1.05
Total staff costs		£11.53
FBC	Haematology	£2.20
U & Es	Chem Path	£5.60
LFT	Chem Path	£3.60
AFP	Chem Path	£1.31
Pregnancy test (5%)	Chem Path	£0.25
TOTAL		**£24.48**

24 weeks post treatment

Staff costs - assumes 20 minutes per appointment with doctor or nurse(alternates - average cost is taken)		£10.48
Overheads for clinic administration @ 10%		£1.05
Total staff costs		£11.53
U & Es	Chem Path	£5.60
LFT	Chem Path	£3.60
HCV RNA	Virology	£11.33
Ultrasound on liver	Radiology	£48.00
AFP (Cirrhotic patients)	Chem Path	£1.31
Pregnancy test (5%)	Chem Path	£0.25
TOTAL		**£81.61**
Total monitoring costs per year		£131.67

Appendix 11 Research in Progress involving PEG*

Study Name and Sponsor	Interventions	Design	Participants (expected enrolments)	Status as of 04/02/2003
Triple Therapies				
South East Regional Office (UK)	1. PEG α-2a + RBV 2. PEG α-2a + RBV + mycophenylate	RCT	n = not reported HCV patients who had failed to respond to previous conventional therapy	Ongoing, End Date: 27/04/2004
Dual Therapies				
US National Institute of Diabetes and Digestive and Kidney Diseases, Hoffman-LaRoche HALT-C (USA)	All patients treated for 6 mo with PEG α-2a + RBV then responders treated additional 6 mo. Non-responders randomised: 1. PEG α-2a for 3.5 yr 2. Discontinue treatment for 3.5 yr	RCT	failed to respond to prior IFN or IFN + RBV treatment	currently recruiting, study completion date May 2006
SciClone Pharmaceuticals (USA)	1. PEG α-2a 180 µg/wk + thymosin alpha 1, 1.6 mg 2x/wk 2. Peg α-2a + placebo	RCT	n=500 HCV *without cirrhosis* who have not responded to previous treatment with IFN or IFN + RBV	currently recruiting
SciClone Pharmaceuticals (USA)	1. PEG α-2a 180 µg/wk + thymosin alpha 1, 1.6 mg 2x/wk 2. PEG α-2a + placebo	RCT	n=500 HCV *with cirrhosis* who have not responded to previous treatment with IFN or IFN + RBV	currently recruiting
Liver Research Trust (UK)	PEG α-2b + RBV "Does a longer course of combination treatment reduce liver fibrosis and prevent further progression of liver disease in patients with chronic Hepatitis C cirrhosis?"	RCT	n=20	end date: 4/1/2003
Columbia	1. PEG α-2a +	RCT	n=not reported	unknown

Presbyterian Medical Center, NY (USA)	RBV 2. IFN α-2a + RBV		treatment naïve	
Monotherapies				
Schering-Plough (USA)	1. PEG α-2a 2. No treatment	RCT (prevention of fibrosis progression)	n=700 patients with moderate to severe fibrosis who failed previous PEG α-2a + RBV treatment	currently recruiting
Schering-Plough (USA)	1. PEG α-2a 2. No treatment	RCT (prevention of disease progression)	n=1000 patients with compensated cirrhosis who failed previous IFN α-2a + RBV treatment	currently recruiting
Trials in Co-infected Populations				
APRICOT (USA)	1. PEG α-2a 180 µg/wk + placebo 2. PEG α-2a 180 µg/wk + RBV 800 mg/day 3. IFN α-2a 3 MIU 3x/wk + RBV 800 mg/day	RCT	n=740 HIV/HCV co-infected, all patients taking stable HAART at entry	unknown
US National Institute of Allergy and Infectious Diseases ACTG 5071 (USA)	1. PEG α-2a + RBV 2. IFN α-2a + RBV	RCT	n= 132 HIV/HCV co-infected	no longer recruiting patients
US National Institute of Allergy and Infectious Diseases 020139 (USA)	1. PEG + RBV 2. highly active anti-retroviral therapy (HAART) for 6 months then PEG + RBV	RCT	n=128 HIV/HCV co-infected	currently recruiting patients
Canadian HIV Trials Network CTN 141 (Canada)	1. PEG 180 µg/wk + RBV 800 mg/day + ddl 400 mg/day + 3TC 300 mg/day	Phase II, open label pilot, single group	n=20 HIV/HCV co-infected	open
US National Institute of Allergy and Infectious Diseases ACTG A5149 (USA)	1. PEG + RBV + adefovir dipivoxil 2. PEG + RBV + placebo	RCT	n=110 triple infected with HBV/HCV/HIV	not yet open for patient recruitment
Other				

Schering-Plough Research Institute (UK)	Assess duration of virological response in those with SVR Assess disease progression in all who completed 24 wk of follow-up	5-year follow-up of patients	n=177 paediatric patients who completed 24 wk follow-up in Hep C treatment trial	ongoing

* Sources searched: Current Controlled Trials – all registers (http://controlled/-trials.com); National Research Register; CenterWatch (http://www.centewatch.com); AIDSinfo (http://www.aidsinfo.nih.gov/clinical_trials/). Searches were conducted 21/01/03 and 04/02/03.

A range of research involving PEG is ongoing. The studies were designed to address a number of different questions. PEG is being combined with drugs other than RBV including mycophenylate and thymosin in three trials. These are trials evaluating possible virological response in patients who had failed to respond to previous conventional hepatitis C treatment. Other studies using dual or monotherapy are evaluating whether the progression of liver disease might be affected by treatment with PEG or combination therapy. The HALT-C trial will treat some patients who fail to respond to PEG + RBV with PEG for 3.5 years. With improved success in treating HIV more attention has turned to treating co-infections such as hepatitis C in patients who have HIV. Five identified trials are evaluating combination therapies including PEG (and sometimes manipulating HIV treatment) in patients with HIV and HCV (and in one case HIV, HCV, and HBV). Finally, one study is conducting 5-year follow-up of paediatric patients who were treated for hepatitis C to evaluate long-term virological response in those who responded and disease progression in others who completed the trial.

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